Guidelines for Reasonable and Appropriate Care in the Emergency Department (GRACE): *Recurrent, Low-risk Chest Pain in the Emergency Department*

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Abstract

Background: Recurrent, low-risk chest pain presents an emergency department clinical dilemma.

Objective: To develop evidence-based guidelines to support patients and clinicians in their decisions about the evaluation and management of recurrent, low-risk chest pain.

Methods: A multidisciplinary guideline panel of emergency physicians, a cardiologist, a patient, and methodologists with varied areas of expertise prioritized initial questions and outcomes; systematic reviews were used when available, and indirect evidence was sought when direct evidence was not available. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to assess the certainty of evidence and strength of recommendations.

Results: The SAEM guideline panel compiled the following recommendations. For adult patients with recurrent, low-risk chest pain: (1) We suggest a single, normal high-sensitivity troponin below a validated threshold to exclude acute coronary syndrome (ACS) within 30 days. (2) For patients with a negative stress test within the previous 12 months, we do not recommend repeat routine stress testing. (3) There is insufficient evidence to recommend admission to the hospital versus admission to the observation unit versus discharge versus home in relation to ACS outcomes within 30 days. (4) and (5) For patients with documented minimally occlusive coronary artery disease (CAD) (<50% stenosis) or

no CAD (0% stenosis) on prior coronary angiography within 5 years, we suggest (<50%)/recommend (0%) referral for expedited outpatient testing versus admission for inpatient evaluation. (6) For patients with prior coronary computed tomographic angiography (CCTA) demonstrating no evidence of coronary occlusion, we suggest no further diagnostic testing other than an electrocardiogram (ECG) and a single, normal high-sensitivity troponin below a validated threshold. (7) and (8) We suggest screening and referral for anxiety/depression management.

Conclusions: These guidelines summarize the evidence and strength of GRACE recommendations regarding eight priority questions of interest with regard recurrent, low-risk chest pain seen in the ED.

Executive summary

Summarized below are the recommendations with comments related to the clinical practice guideline for the evaluation and management of patients with recurrent, low-risk chest pain in the ED. A detailed description of background, methods, evidence summary and rationale that support each recommendation, and research needs can be found online in the full text. Recommendations are labeled as "strong" or "conditional". The word "recommend" indicates strong recommendations and "suggest" indicates conditional recommendations.

Abbreviations:

ACS – acute coronary syndrome; AMI – acute myocardial infarction; CABG- coronary artery bypass graft, CAD- coronary artery disease; CCTA - coronary computed tomographic angiography; ED – emergency department; GRADE - Grading of Recommendations Assessment, Development and Evaluation; MACE - major adverse cardiac events; PCI - percutaneous coronary intervention; PICO - Patient-Intervention-Control-Outcome questions; RCT - randomized clinical trials; SAEM - Society for Academic Emergency Medicine

Recommendations

Recommendation 1: In adult patients with recurrent, low-risk chest pain, we suggest a single, normal 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 negative 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) [Very low level of evidence]

Recommendation 3: In adult patients with recurrent, low-risk chest pain, there is not enough evidence to recommend admission to the hospital versus admission to the observation unit versus discharge home in relation to ACS outcomes within 30 days. (No evidence, Either)

Recommendation 4: In adult patients with recurrent, low-risk chest pain and only minimally occlusive CAD (<50% stenosis) on prior angiography within 5 years, we suggest referral for expedited outpatient testing as warranted rather than admission for inpatient evaluation. (Conditional, Either) [Moderate indirect 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, Either) [Moderate indirect evidence].

Recommendation 6: In adult patients with recurrent, low-risk chest pain and prior coronary computed tomographic angiography (CCTA) with no evidence of occlusion, we suggest no further diagnostic testing other than an electrocardiogram (ECG) and a single, normal high-sensitivity troponin below a validated threshold to exclude ACS for the next two years. (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].

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 aortic dissection, ruptured aortic aneurysm, pericarditis, myocarditis, pulmonary embolism, pneumothorax, pneumonia, and perforated peptic ulcer also cause chest pain. However, only approximately 5% of chest pain visits are diagnosed with these acute life-threatening conditions, with ACS being the most common diagnosis.[5,6] Thus, regardless of the validated instrument used for risk-stratification for ACS (e.g., Thrombolysis In Myocardial Infarction [TIMI] score, History, EKG, Age, Risk factors and Troponin [HEART] score or pathway, Emergency Department Assessment of Chest Pain Score [EDACS]), the rate of patients who present with low- to moderate-risk chest pain is estimated to be between 70-80%.[7,8]

Despite this low prevalence, missed acute myocardial infarction (AMI) and associated adverse events rank as some of the most frequent causes of malpractice lawsuits, and consequently, emergency physicians are loath to miss these conditions.[9,10] Despite this, there is significant variation in the evaluation (diagnostic testing and admission) of these patients. While guidelines and evidence can aid clinicians in the evaluation of low-risk chest pain,[8] significant practice variation persists and is often subject to the available local resources or lack thereof.[11] For example, one recent study found physician-level admission rates varied from 54% to 96% for chest pain patients at a single facility.[12] Recurrent ED

visits for chest pain are common, with up to 40% of patients returning to the ED for chest pain within one year.[13,14] 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 influence of psychosocial factors, without any evolution of underlying physical disease. These factors create a diagnostic dilemma of particular importance for the emergency clinician. The lack of guidelines specific to the 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 it 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 (APPs)) 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. SAEM provided financial support for the development of this guideline.

Figure 1: A schematic view of the GRADE approach for synthesizing evidence and developing recommendations. [FIGURES and TABLES found starting on page 43]

Group interaction and processes

Starting in May 2019, the panel met regularly through in-person, online, and telephone meetings. The methodologists attended 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 physicians with relevant publications in the field. An introduction to the GRADE process of creating and weighting clinical recommendations was delivered to all panel members. [INSERT LINK TO TRAINING VIDEO]

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.[15] Panel members prioritized questions and patient-important outcomes such as 30-day major adverse cardiac events (MACE) defined as acute myocardial infarction (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:

Based on the advice of our medical librarian, a single strategy for recurrent chest pain was conducted. 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 search found 5,252 titles for review. The titles and abstracts were reviewed independently and in triplicate by the three methodologists. A total of 334 full-text articles were retrieved and reviewed in triplicate, and 80 eligible studies were matched with each PICO question. Six additional articles were provided by a content expert and were matched with the appropriate questions. A total of 38 other articles were found by content experts with indirect evidence and were used to create these guidelines. See **Figure 2** for PRISMA flow diagram.

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.[16] The certainty of evidence was assessed using the GRADE approach.[17] 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: Rating the quality of evidence using the GRADE methodology

Table 1: Interpretation of strong and weak recommendations for patients, clinicians, and healthcare policymakers.[18]

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.[19,20] 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.[21]

The GRACE-1 writing committee identified the eight questions summarized in **Box 1**.

Box 1: Key questions

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

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

3- (P) In adult patients with recurrent, low-risk chest pain, (I) does 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?

In deriving those questions, GRACE-1 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 (and other scores validated in the ED setting such as the HEART Pathway or TIMI score) for disease-related poor outcomes within 30 days.

It should be stated that 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.[22] Use of the HEART score yields a ~2% major adverse cardiac event rate among patients with a low-risk score of 0-3.[22,23] In derivation work, HEART score incorporated only 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 its reproducibility and reliability.[2] In contrast, the HEART Pathway is an accelerated diagnostic protocol, which uses a modified HEART

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. The HEART Pathway is best used as a clinical decision support tool integrated into the electronic health record. 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.[24,25] One important note: the term "low risk" in these guidelines 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.[26]

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**.

Box 2: Recommendations

Recommendation 1: In adult patients with recurrent, low-risk chest pain, we suggest a single, normal 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 negative 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) [Very low level of evidence]

Recommendation 3: In adult patients with recurrent, low-risk chest pain, there is not enough evidence to recommend admission to the hospital versus admission to the observation unit versus discharge home in relation to ACS outcomes within 30 days. [No evidence]

Recommendation 4: In adult patients with recurrent, low-risk chest pain and only minimally occlusive CAD (<50% stenosis) on prior angiography within 5 years, we suggest referral for expedited outpatient testing as warranted rather than admission for inpatient evaluation. (Conditional, Either) [Moderate indirect 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, Either) [Moderate indirect evidence].

Recommendation 6: In adult patients with recurrent, low-risk chest pain and prior coronary computed tomographic angiography (CCTA) with no evidence of occlusion, we suggest no further diagnostic testing other than an electrocardiogram (ECG) and a single, normal high-sensitivity troponin below a validated threshold to exclude ACS for the next two years. (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].

Question 1

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

Summary of the evidence

There were zero 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[27-35] 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. Thus, insufficient evidence exists to recommend for or against a single conventional troponin measurement in patients with recurrent, low-risk chest pain. 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. These studies did not address the "recurrence" of chest pain, so we expect 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.

Benefits

The most substantial benefit to both patients and hospitals in performing a single troponin is shorter ED length of stay.[36] 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 1,000 patients (95% CI 2.0 to 4.8 per 1,000) 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 emergency physicians.[10] 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, and physicians are using single conventional and high-sensitivity cardiac troponin testing in clinical practice.[37,38] 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.

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 modified HEART score.

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

Table 2: Question 1 evidence table

Question 2

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

Summary of the evidence

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.[39,40] 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.[41] This study sought to compare the incidence of MACE at 30 days between patients who completed an outpatient stress test within 3 days, 4 to 30 days, or not at all.

Among the three studies with indirect evidence, zero out of 4,906 ED patients (0%) with chest pain died at 30 days, while 91 out of 4,906 patients (1.9%) experienced a non-fatal, significant cardiac event. These significant cardiac events included myocardial infarction, ventricular fibrillation, acute pulmonary edema requiring intubation, cardiogenic shock, coronary revascularization (i.e. percutaneous coronary intervention or coronary artery bypass graft), and significant coronary artery disease on coronary angiogram.

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.[42-45] 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.[39,40] 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 three days, nor within 30 days, compared with not undergoing a stress test at all.[41]

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.[39]

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.[46] 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.[47] Thus,

shared decision-making may be reasonable in this clinical scenario.[48] 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.[49]

It is important to note that different types of cardiac stress testing (e.g., exercise, pharmacological, nuclear, echocardiographic) exhibit different accuracies,[50] and thus a different type of stress testing or other evaluation modality such as CCTA or angiography may be considered if there is concern for false-negative results on a previous stress test. 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.[51] 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 negative stress testing within the last 12 months.

Recommendation 2: In adult patients with recurrent, low-risk chest pain, and a negative 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) [Very low level of evidence]

Table 3: Question 2 evidence table

Question 3

In adult patients with recurrent, low-risk chest pain, does 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

Zero 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 less than 1%.[25] Healthcare costs associated with the ED evaluation of chest pain is 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.[52-54]

Recommendation 3: In adult patients with recurrent, low-risk chest pain, there is not enough evidence to recommend admission to the hospital versus admission to the observation unit versus discharge home in relation to ACS outcomes within 30 days. [No 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 clear-cut 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.[55,56] In fact, some studies suggest that high rates of normal or negative diagnostic catheterizations indicate opportunities for improved patient selection for the procedure.[57] 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.[49,58] 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 one summary meta-analysis with minimal risk of bias, and a number of retrospective chart reviews. Only the meta-analysis by Radico[59] (2018, 54 studies with 35,039 patients, mean follow-up five years) separately analyzed those patients with non-obstructive CAD (<50%) versus those with 0% stenosis (which is the next question addressed by this guideline). However, heterogeneity was high; in this meta-analysis (I^2 = 91%), limiting the utility of pooling data for meta-analysis (though this was mitigated with random-effects analysis). The remaining observational

studies did not separate and analyze those without any stenosis versus those with <50% stenosis.[60-64] The data available suggest that the likelihood of non-fatal MI (3.6%) or all-cause death (4.1%) within five years is low in this group. (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.

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 (3.6%) or all-cause death (4.1%) within 5 years are 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.

Recommendation 4: In adult patients with recurrent, low-risk chest pain and only minimally occlusive CAD (<50% stenosis) on prior angiography within 5 years, we suggest referral for expedited outpatient testing as warranted rather than admission for inpatient evaluation. (Conditional, Either) [Moderate indirect 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 (2.88%) or all-cause death (2.97%) within 5 years are low in this group. The evidence informing this question is based on one summary meta-analysis with minimal risk of bias, and a number of retrospective studies. Only the meta-analysis by Radico [59] (2018; see limitations described in PICO #4) separately analyzed those patients with non-obstructive CAD (<50%; PICO Question #4) versus those with 0% stenosis. The remaining observational studies did not separate and analyze these two groups. [60-64] (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.[47]

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.[65]

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, Either) [Moderate indirect 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 zero 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 vs. 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 CTA strategy used for evaluating low to intermediate-risk patients as opposed to reporting outcomes based on the degree of stenosis present on the CTAs. Two studies that included patients who underwent outpatient evaluation for possible myocardial ischemia reported long term results. The CONFIRM Registry[66] 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[67], 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.[67] 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.

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.[68-74] This risk is increased with repeated CT scans, female sex and younger age.[74-76] 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.[77] Simulation modeling has estimated the lifetime cancer risk for a standard cardiac CT scan to vary from 1 in 143 for a 20-year-old woman to 1 in 3261 for an 80-year-old man.[78] 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 ischemic evaluation other than a troponin and ECG for patients with recurrent, low-risk chest pain after a negative CCTA within two 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 negative prior CCTA, we suggest no further diagnostic testing other than an ECG and a single, normal high-sensitivity troponin below a validated threshold to exclude ACS for the next 2 years. (Conditional, For) [Moderate level of evidence]

Table 4: Question 6 Evidence Table

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.[79] 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 (OR 2.11; 95% CI 1.18-3.79), as well as increased ED return visits and increased healthcare use.[79] However, this study had a small sample size (n=365). The depression screening tool used in this study was the validated eight-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 28.[80]

For anxiety screening**,** three studies were included to provide indirect evidence.[79,81,82] 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[79] 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[81] found increased risk of CP recurrence with an OR of 2.36 (95% CI 1.09-5.15). Regarding return ED visits, two studies[79,81] showed increased risk of ED return in patient screening positive for anxiety, while one study[82] showed no difference in return visits. Regarding overall healthcare use, one study[82] showed no significant difference among the two groups (18.2% versus 24.8%).

Kim et al used the clinical anxiety scale (CAS)[83], a 25-item self-administered tool to determine anxiety symptoms over the two 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.[84] Finally, Schwarz et al used the validated generalized anxiety disorder 7-item scale (GAD-7) to identify anxiety symptoms over the prior two weeks with scores ≥ 15 denoting severe anxiety.[85] (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 7-25 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. Additionally, when taking screening into account, clinicians will need to guard against premature closure and anchoring bias,

744 which represent two types of cognitive error that can threaten patient safety by failing to
745 consider potentially life-threatening etiologies of chest pain attributed to psychiatric
746 causes.[26]

747 ***Decision criteria and additional considerations***

748 Currently, our healthcare systems and EDs are encouraged by the Joint Commission to
749 implement universal screening for suicidality, for all patients, irrespective of whether they
750 are presenting with psychiatric complaints of suicidality.[86] This is an acknowledgment of
751 the fact that it is well-established that undiagnosed or under-addressed psychological
752 factors, such as anxiety and depression, are prevalent (possibly greater than 40%) and may
753 complicate or contribute directly to medical problems and somatic complaints.[87] However,
754 it must be stated that the primary imperative of emergency medicine is to evaluate for and
755 manage conditions that pose immediate threats of morbidity and mortality. Thus, of
756 paramount relevance to EM providers is the notion that "EM should not take on any non-
757 core initiatives until ED care itself is adequately resourced."[88] Therefore, the barriers to
758 screening for psychological conditions in some cases and ED environments are myriad: 1)
759 optimal timing regarding when in the time course such screening is appropriate and
760 whether it can or should occur in triage or in the treatment area; 2) what specific screening
761 tool(s) should be used and how should they be administered (e.g., verbal, paper, electronic)
762 and who should administer (e.g., self-administered, nursing personnel, social workers, ED
763 providers); and 3) should screening be universal or triggered by an overt action such as a
764 physician order?

765 Additionally, the decisions about how to deal with the results of this screening results pose
766 serious consideration (i.e. how are results provided to both clinicians and patients and how

767 does this translate into the next step in care). There also must be an acknowledgment of the
768 role of gender and race in the historical context of labeling patients as hysterical in the case
769 of females or underdiagnosis in the case of minorities.[89,90] Finally, it has been documented
770 that EM providers do not often address these psychological issues even when informed,
771 which may be a result of the lack of sufficient available resources, such as directed
772 outpatient psychiatric follow-up.[91,92] Thus, there is a need to determine what the
773 responsibility of the treating clinician is with regard to specifically addressing the screening
774 results, especially in the landscape of medicolegal considerations. While individual
775 providers are free to use their clinical judgment and pursue targeted screening for their
776 patients, for the reasons outlined above, the decision to embrace a more comprehensive
777 screening paradigm should be made at the level of the department where appropriate
778 system resources should be coordinated to support such an effort.

779 ***Conclusions and research needs***

780 Indirect evidence from a single site prospective observational study found increased chest
781 pain recurrence, ED utilization, and healthcare use among patients screening positive for
782 clinically relevant depression among a population of low-to-moderate risk chest pain
783 patients. While indirect evidence from 3 studies found that, despite a high prevalence of
784 clinically relevant anxiety among low-to-moderate chest pain patients, there are mixed
785 results for this association with chest pain recurrence, ED utilization and healthcare use.
786 To provide specific direct evidence to answer this question, prospective studies are needed
787 which 1) include a measure of recurrent chest pain visits prior to enrollment; 2) include a
788 clear description of ACS risk stratification in the ED and specifically include those with
789 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; 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]

Table 5: Question 7 Evidence tables

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 [93] evaluated psychological interventions in 17 RCTs with 1,006 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 three months following the intervention (RR 0.70; 95% CI 0.53 to 0.92). There was an increase in the number of chest pain-free days up to three months following the intervention (mean difference [MD] 3.00; 95% CI 0.23 to 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.

Wang et al.[94] evaluated antidepressants for symptomatic management of functional chest pain (defined as normal coronary angiography). The authors included 7 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 to 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 three 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].

Table 6: Question 8 evidence table

General issues necessary for correct interpretation and implementation of recommendations

Assumed values and preferences

Limited data exist on patient preferences regarding the management of recurrent, low-risk chest pain. In one 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.[95,96] 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

884 physician's recommendation for cardiac interventions.[49] At 30-day follow up, women were
885 less likely than men to receive any cardiac diagnostic testing and to undergo cardiac
886 catheterization.[49] Taken together, these data highlight the importance of shared decision-
887 making and considering patients' values and preferences in the ED management of low-
888 risk chest pain.[65] Although the panel acknowledges that the method of communicating
889 with patients about their chest pain was not evaluated as a specific PICO question.
890
891 **Plans for updating these guidelines**
892 Evidence is constantly growing. These guidelines should be updated within 5 years, or
893 when significant new relevant high-quality research requires reassessment and revision of
894 the relevant recommendation(s). Adoption of these guidelines should be tailored to local
895 policies and practices. Availability of cardiology consultation, stress test, CCTA and type
896 of troponin test might differ in each hospital.
897
898 **Monitoring criteria for Audit/Feedback of Implementation**
899 Based on the recommendations of this guideline being Conditional with Very
900 Low/Low/Moderate levels of supporting evidence, we cannot offer monitoring criteria for
901 audit/feedback purposes with prospective implementation of any/all of these
902 recommendations at this time. Should future evidence and updates warrant a Strong
903 recommendation for an intervention with High level supporting evidence, we will suggest
904 potential monitoring/audit criteria at that time.
905
906
907

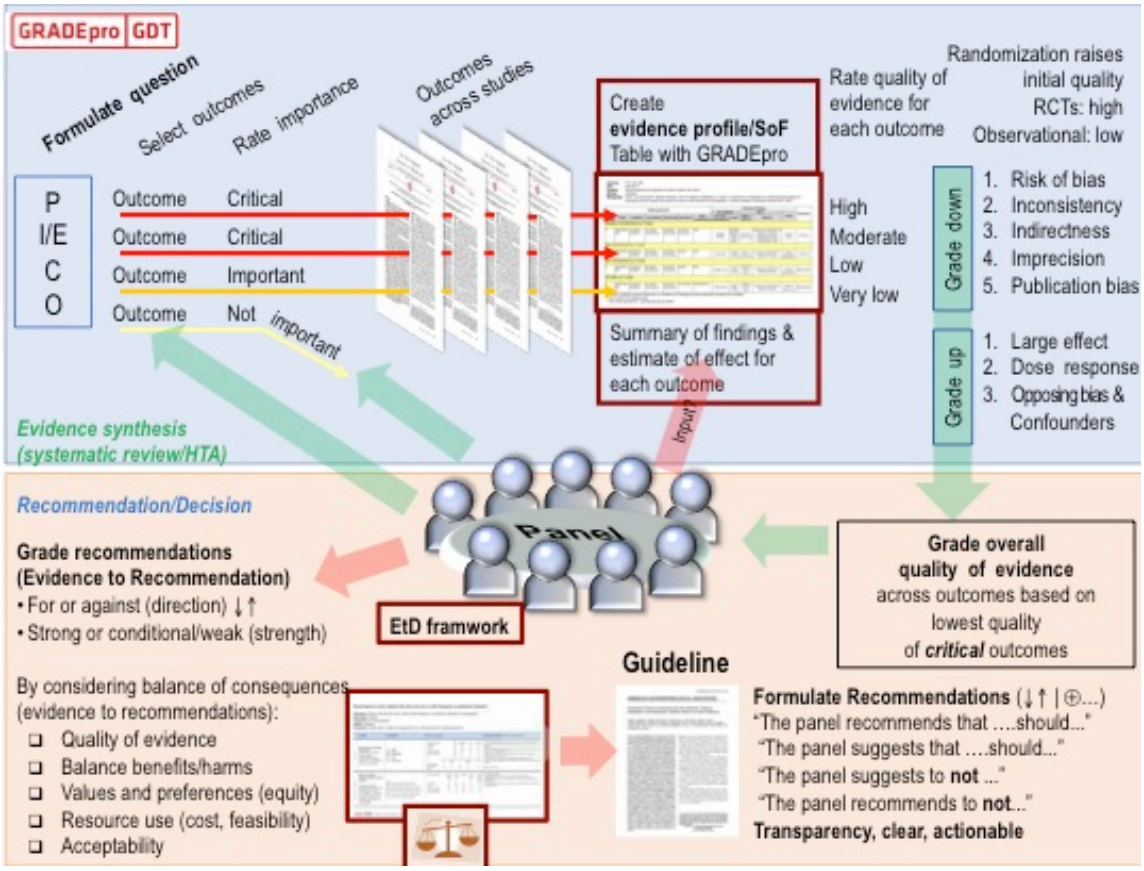
Conclusions

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.

References (placeholder, currently at very end of document)

Figures and Tables

Figure 1: A schematic view of the GRADE approach for synthesizing evidence and developing recommendations.

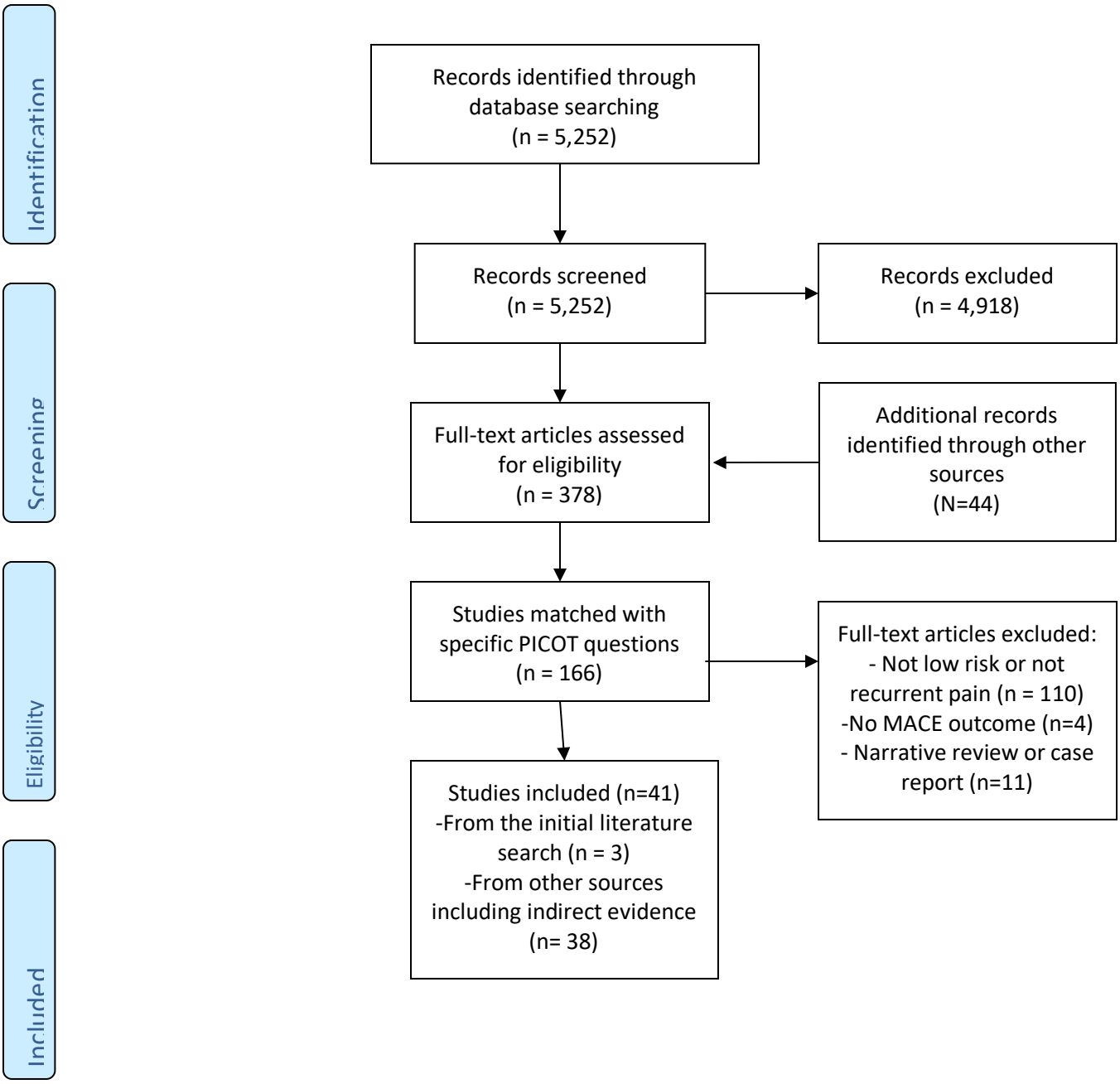


Footnote: The upper half describe steps in the process common to systematic reviews and making health care recommendations and the lower half describe steps that are specific to making recommendations including steps from panel members to make recommendations.

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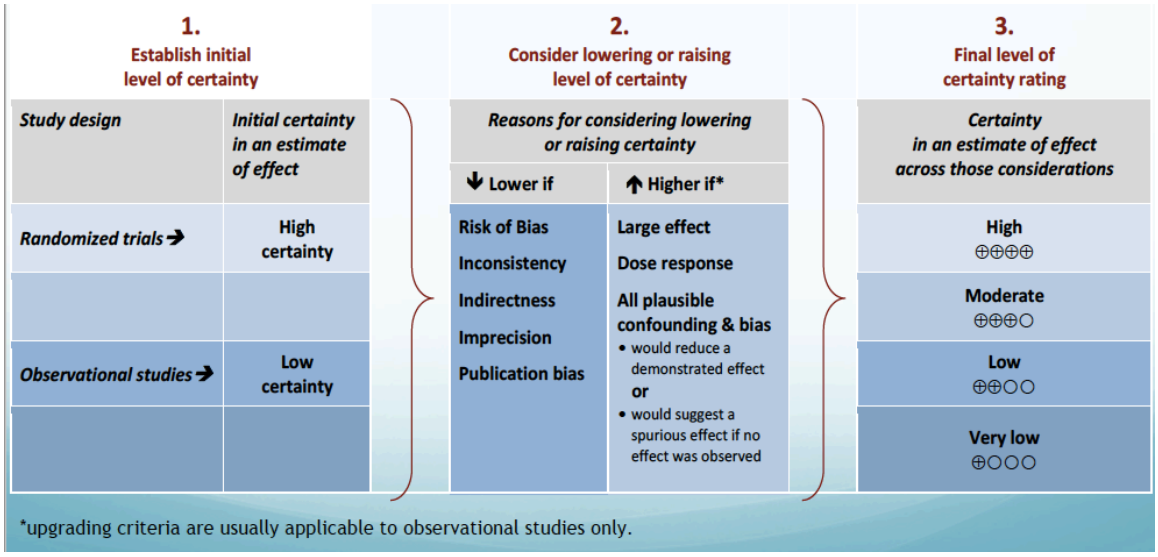
PRISMA Flow Diagram

929
930



931 Figure 2. Rating the quality of evidence using the GRADE methodology

932



933

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935

936 Table 1: Interpretation of strong and weak recommendations for patients, clinicians, and
937 healthcare policymakers.

Table 1. 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	Policy making will require substantial debates and involvement of many

	for the use as performance indicators.	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.

938 *Reproduced with permission from the GRADE Handbook.

939 https://gdt.gradepro.org/app/handbook/handbook.html#h.svwngs6pm0f2 [18]

940

Table 2: Evidence table - Question 1

Question: Course of Single troponin in low-risk chest pain over 30 days AMI and MACE outcomes

Certainty assessment							№ of patients	Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Single troponin	Outcome rate (95% CI)		
9	observational studies	not serious [a]	not serious	serious [b]	not serious	strong association	72/15717 (0.5%) [c]	3.4 per 1,000 patients (2.0 to 4.8 per 1,000)	⨁⨁◯◯ LOW	IMPORTANT

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 vs 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)

950 Table 3: Question 2 evidence table

951 **Question**: Repeat provocative stress testing compared to No stress testing for In adult patients with recurrent, low-risk chest pain, and negative or non-diagnostic stress testing within the last 12 months
952

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ 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)		
Death (follow up: 30 days)												
2	randomised 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 studies	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	randomised trials	not serious	not serious	serious [a]	not serious	none	4/1004 (0.4%)	4/504 (0.8%)	**OR 0.50** (0.13 to 2.00)	**4 fewer per 1,000** (from 7 fewer to 8 more)	⨁⨁⨁◯ MODERATE	IMPORTANT
Significant CAD												
1	randomised trials	not serious	not serious	serious [a]	not serious	none	36/1004 (3.6%)	15/504 (3.0%)	**OR 1.20** (0.61 to 2.17)	**6 more per 1,000** (from 11 fewer to 33 more)	⨁⨁⨁◯ MODERATE	IMPORTANT
MACE (follow up: 30 days)												
2	randomised trials	serious [b]	not serious	serious [a]	not serious	none	27/2549 (1.1%)	5/849 (0.6%)	**OR 1.81** (0.69 to 4.71)	**5 more per 1,000** (from 2 fewer to 21 more)	⨁⨁◯◯ LOW	CRITICAL

953

954 **CI:** Confidence interval; **OR:** Odds ratio

955 a. Not recurrent low-risk chest pain and does not assess this outcome for those with previous stress testing within 12 months.
956 b. One non-randomized interventional trial
957

958 Table 4: Question 6 Evidence Table

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MACE	NO MACE	Relative (95% CI)	Absolute (95% CI)	
Coronary CT with no disease (follow-up 30 days to 2 years) MACE											
6	Observational studies	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	randomised 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	randomised trials	Not serious	not serious	serious	serious [d]	none	1	828			⊕⊕⊕◯ MODERATE
Coronary CT with no disease (follow-up 2 years) MACE non-ED patients											
2	Observational studies	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

Table 5: Question 7 Evidence tables

PICOT #7a Depression

Question: Depression screening compared to no depression for adult patients with recurrent low-risk chest pain

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Depression screening	no depression	Relative (95% CI)	Absolute (95% CI)		
Healthcare use/30 day hospital return												
1 [a]	observational studies	serious [b,c]	not serious [d]	serious [e]	not serious [f]	none [g]	5/131 (3.8%)	0/234 (0.0%)	**OR 19.60** (1.08 to 357.60) [h]	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	
Return ED visits												
1	observational studies	serious [b,c]	not serious [d]	serious [e]	not serious [f]	none	10/131 (7.6%)	0/234 (0.0%)	**OR 37.50** (2.18 to 644.30) [h]	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	
Chest pain recurrence												
1	observational studies	serious [b,c]	not serious [d]	serious [e]	not serious [f]	none			**OR 2.11** (1.18 to 3.79)	**2 fewer per 1,000** (from 4 fewer to 1 fewer)	⨁◯◯◯ VERY LOW	
Healthcare use/PCP follow up												
1 [a,g]	observational studies	serious [b]	not serious	not serious	not serious	none	91/131 (69.5%)	151/234 (64.5%)	**OR 1.08** (0.77 to 1.51) [h]	**17 more per 1,000** (from 62 fewer to 88 more)	⨁◯◯◯ VERY LOW	

CI: Confidence interval; **OR:** Odds ratio

a. Kim et al.
b. Kim 2017: Stratified by recurrent CP vs NRCP not by anxiety -depression screening status. Selection bias of subjects admitted to obs 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: 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.
f. Imprecision: The decision will not differ across boundaries of the CI.
g. *** question: How we define healthcare use? Could be 30-day hospital return (5/131 vs 0/234) or follow up with provider (91/131 vs 151/234)
h. OR were not provided in the original article

PICOT #7b Anxiety

Question: Anxiety screening tools compared to no screening for recurrent low-risk chest pain

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	anxiety screening tools	no screening	Relative (95% CI)	Absolute (95% CI)		
Healthcare use/PCP follow up												
1 [a]	observational studies	serious [b]	not serious	serious [b]	serious [c]	none	4/22 (18.2%)	32/129 (24.8%)	**OR 0.73** (0.24 to 2.28)	**54 fewer per 1,000** (from 175 fewer to 181 more)	⨁◯◯◯ VERY LOW	
ED return												
2	observational studies	serious [d]	not serious	not serious	not serious	none			**OR 3.22** (1.53 to 6.80)	**3 fewer per 1,000** (from 7 fewer to 2 fewer)	⨁◯◯◯ VERY LOW	
Chest pain recurrence												
1 [e]	observational studies	serious [f]	not serious	not serious	serious [g]	none	38/56 (67.9%)	25/53 (47.2%)	**OR 1.59** (0.80 to 3.79)	**115 more per 1,000** (from 55 fewer to 300 more)	⨁◯◯◯ VERY LOW	

CI: Confidence interval; **OR:** Odds ratio

a. Schwarz et al.
b. Schwarz 2015: 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 3 studies and representative of the population of interest. The outcomes are mostly self-reported. Lost of follow up.
e. Musey et al.
f. Musey 2018: Follow up assessed by pt report and chart review. Potential recall bias.
g. Musey: Follow up data available in only 109 subjects.

989 Table 6: Question 8 evidence table

990 **Question 8**: Referral for anxiety/depression compared to no referral for adult patients with recurrent low-risk chest pain and high risk of anxiety/depression
991

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	referral for anxiety/depression	no referral	Relative (95% CI)	Absolute (95% CI)		
Psychotherapy Interventions vs Control, Any chest pain (follow up: 30 days)												
3	randomised 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 to 0.92)**	**278 fewer per 1,000 (from 436 fewer to 74 fewer)**	⊕⊕◯◯ LOW	
Psychotherapy Interventions vs Control, Any chest pain (follow up: range 3												
2	randomised 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 to 0.76)**	**383 fewer per 1,000 (from 514 fewer to 224 fewer)**	⊕⊕◯◯ LOW [d]	
Psychotherapy Interventions vs Control, Chest pain frequency (follow up: 3 months												
7	randomised trials	serious [a,b]	serious [e]	not serious	not serious	none	154	140	-	MD **2.26 lower (4.41 lower to 0.12 lower)**	⊕⊕◯◯ LOW	
Psychotherapy Interventions vs Control, Chest pain frequency (follow up: range 3 months to 12 months)												
4	randomised trials	serious [a,b]	not serious	not serious	serious [f]	none	84	80	-	MD **0.81 lower (2.35 lower to 0.74 higher)**	⊕⊕◯◯ LOW	
Antidepressants vs Placebo, Reduction of chest pain												

7	randomised trials	serious [g]	serious [h]	not serious	not serious	none	161	158	-	MD **1.26 lower (2.43 lower to 0.13 lower)**	⊕⊕◯◯ LOW	

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

a. In 10 studies there was a low-risk of random sequence generation and/or selection bias. In 7 there was unclear risk for both of these biases. In studies where there was a medical aspect to the intervention, the patients were blinded to medication or placebo. However, due to the nature of the main interventions of interest (normally counselling or CBT), it was impossible to blind the people delivering the treatment as to whether the participant was in the intervention or control arm. In addition, in 3 studies the blinding of participants was forbidden by the local ethics committee because of issues in obtaining fully informed consent. For this reason, the SR considered all studies to be at high risk of performance bias. As outcomes were largely assessed by self-reports, and the patients were at least in part not blinded to the intervention, the authors of the SR judged most studies at high risk of outcome assessment bias.

b. One exception was van Beek 2013, 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 analysed data based on ITT analysis. We considered 3 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 of selective reporting because they did not clearly state the outcomes of interest.

c. There is significant differences in results between individual studies. High I-squared 94%. Small sample studies.

d. Decision will differ if the truth is in the lower vs upper boundary of the CI.

e. Large heterogeneity I-squared 94%

Appendices

Appendix 1: Data Sources and Search Strategies

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 librarian with input from the study's principle investigator. Controlled vocabulary supplemented with keywords was used to search for studies on recurrent chest pain. The full search strategy is presented here.

Database(s): **Ovid MEDLINE(R) 1946 to Present and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) Daily, EBM Reviews - Cochrane Central Register of Controlled Trials** July 2019**, EBM Reviews - Cochrane Database of Systematic Reviews** 2005 to August 15, 2019**, Embase** 1974 to 2019 August 14

Search Strategy:

Supplementary Table 1: Appendix 1 search strategies

#	Searches	Results
1	((recidiv* or recur or recurred or recurren* or recurring or recurs or regenerat* or relaps* or reoccur* or "re-occur*") adj3 (angina or "chest pain*")).ti,ab,hw,kw.	6606
2	exp Recurrence/	359359
3	exp Chest Pain/	142736
4	2 and 3	4020
5	1 or 4	9966
6	limit 5 to English language [Limit not valid in CDSR; records were retained]	8450
7	6 not ((exp animals/ or exp nonhuman/) not exp humans/)	8433
8	from 7 keep 1-6000	6000
9	from 7 keep 6001-6201	201
10	remove duplicates from 8	5051
11	remove duplicates from 9	201
12	10 or 11	5252

SCOPUS

1	TITLE-ABS-KEY (((recidiv* OR recur OR recurred OR recurren* OR recurring OR recurs OR regenerat* OR relaps* OR reoccur* OR "re-occur*") W/3 (angina OR "chest pain*")))

2	INDEX(embase) OR INDEX(medline) OR PMID(0* OR 1* OR 2* OR 3* OR 4* OR 5* OR 6* OR 7* OR 8* OR 9*)
3	#1 and not #2
4	DOCTYPE(ed) OR DOCTYPE(bk) OR DOCTYPE(er) OR DOCTYPE(no) OR DOCTYPE(sh) OR DOCTYPE(ch)
5	#3 and not #4
6	LANGUAGE(english)
7	#5 and #6

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Appendix 2: Evidence Retrieval, Assessment, and Synthesis for Question #1

Included Studies: 5,252 titles reviewed, 338 articles selected for full text review, 4 studies were included for PICO question #1. Three of the 4 studies were abstracts only, and none met full criteria for inclusion.

Additional search 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 the following studies that evaluated a single troponin in ED patients with low-risk chest pain with 30-day MACE outcome:

A. Bandstein, *et al.* Undetectable high-sensitivity cardiac troponin T level in the emergency department and risk of myocardial infarction. J Am Coll Cardiol. 2014 Jun 17;63(23):2569-2578.[27]

Summary: This retrospective, single-center cohort study included 14,636 patients with chest pain and ≥1 hs-cTnT measurement. Among patients with an initial hs-cTnT <5 ng/L and no ischemia on ECG, rate of 30-day MI was 0.17% and risk of 30-day death was 0.02%. Among patients with initial hs-cTnT 5-14 (regardless of ECG findings), rate of 30-day MI was 3.08% and risk of 30-day death was 0.41%.

Conclusion: This study supports the use of a single hs-cTnT <5 ng/L and a nonischemic ECG to exclude 30-day MACE.

Low-risk patients: Non-ischemic ECG

Limitations: This was a single university hospital ED. ECGs were reviewed for ischemia only in patients with hs-cTnT <5 ng/L; patients with an initial hs-cTnT 5-14 ng/L were not differentiated by ECG findings or overall cardiovascular risk. The study did not evaluate

whether non-ischemic ECG and initial hs-cTnT 5-14 ng/L is sufficient for ruling out 30-day MACE.

B. Cullen, *et al.* Validation of high-sensitivity troponin I in a 2-hour diagnostic strategy to assess 30-day outcomes in emergency department patients with possible acute coronary syndrome. J Am Coll Cardiol. 2013 Oct 1;62(14):1242-1249.[28]

Summary: This study was a secondary analysis of patients from two prospective cohort studies (ADAPT [n=1,635] and APACE [n=909]) to evaluate diagnostic protocols: 1) TIMI risk score; 2) ECG; and 3) hs-cTnI at 0 and 2 hours. Among "low-risk" patients defined by TIMI ≤1, normal ECG, and normal hs-cTnI at 0 and 2 hours, sensitivity in the primary ADAPT cohort was 99.2 (95% CI: 97.1 to 99.8) and in the secondary APACE cohort was 99.4% (95% CI: 96.5 to 100). TIMI score 0 - which includes a single hs-cTnI < 26.2 ng/L - had a sensitivity of 98.4% (95% CI 95.9-99.4%) in the ADAPT cohort and 99.4% (95% CI 96.5-100%) in the APACE cohort for 30-day MACE.

Conclusion: An early-discharge strategy using an hs-TnI assay and TIMI score ≤1 had similar safety as previously reported.

Low-risk patients: The study's "low-risk" group definition required serial troponins, but their patients with TIMI 0 meet our definition of a low-risk group.

Limitations: This study focused on 0- and 2-hour serial hs-cTnI algorithm rather than single troponin.

C. Datlow, *et al.* Troponin Limit of Detection Plus Cardiac Risk Stratification Scores to Rule Out Acute Myocardial Infarction and 30-Day Major Adverse Cardiac Events in ED Patients. Crit Pathw Cardiol. 2017 Dec;16(4):142-146.[29]

Summary: This retrospective cohort study included 333 ED patients defined as low-risk by the HEART score and 143 patients defined as low-risk by the ACS Pretest Probability Assessment <2% who were undergoing serial conventional cTnI testing. No low-risk patients with an initial conventional cTnI below the limit of detection (LOD) had index AMIs (sensitivity 100%, 95% CI 93-100%) or 30-day MACE (sensitivity 100%, 95% CI 96-100%).

Conclusion: This study supports the use of a single conventional troponin at the LOD cut point in low-risk patients to exclude AMI and 30-day MACE.

Low-risk patients: HEART score ≤3; ACS Pretest Probability Assessment <2%

Limitations: This is a small, single-center, retrospective study that relied on chart review to ascertain 30-day outcomes. Patients with missing outcome data were excluded. Duration of symptoms prior to ED presentation was not reported, and it is unknown whether the findings can be generalized to patients who present early after symptom onset.

D. Kavask, *et al.* Clinical chemistry score versus high-sensitivity cardiac troponin I and T tests alone to identify patients at low or high risk for myocardial infarction or death at presentation to the emergency department. CMAJ. 2018 Aug 20;190(33):E974-E984.[30]

Summary: This secondary analysis of four cohort studies (n=4,245 total) evaluated the clinical chemistry score (CCS) with both hs-cTnT and hs-cTnI to predict 30-day MI or death. The hs-cTnI CCS score of 0 had a sensitivity of 100% (95% CI 99.5%–100%), and the hs-cTnT CCS had a sensitivity of 99.9% (95% CI 99.2%–100%). The CCS had better

sensitivity than hscTn alone (hs-cTnI < 5 ng/L: 96.6%, 95% CI 95.0%–97.8%; hs-cTnT < 6 ng/L: 98.2%, 95% CI 97.0%–99.0%).

Conclusion: The CCS score 0 was more sensitive than hs-Tn alone for 30-day MI or death.

Low-risk patients: Defined as CCS 0, which includes hs-cTnT <8 ng/L or hs-cTnI <4 ng/L as well as glucose <100 mg/dL and eGFR ≥90 mL/min/1.73m^2.

Limitations: This study was conducted in non-US populations. eGFR may not be reported to clinicians at levels necessary to calculate CCS, and CCS is a not a familiar risk stratification tool for clinicians.

E. McCord, *et al.* Prognostic Utility of a Modified HEART Score in Chest Pain Patients in the Emergency Department. Circ Cardiovasc Qual Outcomes. 2017 Feb;10(2).[31]

Summary: This prospective, multicenter cohort study (prespecified sub-study of TRAPID-AMI) evaluated the modified HEART score plus hs-cTnT to identify a group of patients at low-risk for 30-day MACE, defined as AMI or all-cause death (no revascularization). Of the 1,282 patients studied, 413 had a modified HEART score ≤3 and hs-cTnT <14 ng/L on initial and serial draws. Patients with modified HEART score ≤3 and T0 hs-cTnT <14 ng/L had a 30-day MACE rate of 0.9%. 30-day MACE rates were lower when hs-cTnT was drawn at 1 hr, 2, hrs, and ≥4 hrs (0.6%, 0.4%, and 0.2%, respectively). When a modified HEART score ≤3 was combined with a T0 hs-cTnT <12 ng/L and 1-hour delta <3 ng/L, the 30-day MACE rate was 0.2%

Conclusion: The authors conclude that a 1-hour delta protocol using hs-cTnT plus modified HEART score identifies patients at low-risk of MACE. If a 1% threshold for 30-

day MACE is used, the study supports a single hs-cTnT <14 ng/L in patients with a modified HEART score ≤3.

Low-risk patients: Modified HEART score ≤3

Limitations: The study population came primarily from non-US sites and used European cutpoint for hs-cTnT.

F. Mokhtari, *et al.* A 0-Hour/1-Hour Protocol for Safe, Early Discharge of Chest Pain Patients. Acad Emerg Med. 2017 Aug;24(8):983-992.[32]

Summary: This secondary analysis of a prospective, observational study evaluated the diagnostic accuracy of an ADP using a 0/1-hr hs-cTnT strategy with TIMI score and ECG to exclude 30-day MACE in 1,020 patients. The combination of an adapted TIMI score ≤1, a nonischemic ECG, and either a 0-hour hs-cTnT < 5 ng/L or a 0-hour hs-cTnT < 12 ng/L combined with a 1-hour increase < 3 ng/L identified 432 (42.4%) patients as very low-risk with a negative predictive value of 99.5% (95% CI 98.3%–99.9%) and a negative likelihood ratio of 0.04 (95% CI = 0.01–0.14) for 30-day MACE.

Conclusion: The ADP plus TIMI ≤1 and nonischemic ECG identified patients with sufficiently low-risk of MACE that further cardiac testing is not necessary.

Low-risk patients: TIMI ≤1 and nonischemic ECG

Limitations: This study was conducted at a single hospital in Sweden.

G. Sandoval, *et al*. Myocardial Infarction Risk Stratification With a Single Measurement of High-Sensitivity Troponin I. J Am Coll Cardiol. 2019 Jul 23;74(3):271-282. [33]

Summary: This multicenter, prospective, observational study conducted at 29 US sites (HIGH-US) evaluated two hs-cTnI assays for the prediction of index AMI and AMI or death at 30 days. They compared the LOD, limit of quantification (LOQ), and other thresholds. An optimized threshold of <5 ng/l identified almost one-half of all patients as low-risk, with sensitivities of 98.6% (95% CI 97.2% to 100%) and NPVs of 99.6% (95% CI 99.2% to 99.9%) for acute MI or death at 30 days across both hs-cTnI assays. In combination with a nonischemic ECG (Online Table 7), single-measurement rule-out strategies using either the analytical or optimized concentration thresholds resulted in sensitivities and NPVs >99% for 30-day AMI or death.

Conclusion: A single hs-cTnI <5 ng/L at presentation identifies patients at low-risk for 30-day AMI or death.

Low-risk patients: Nonischemic ECG

Limitations: Overall population is relatively high risk (38% with known CAD, 70% with HTN); unclear whether nonischemic ECG truly represents low-risk population.

H. Tan, *et al.* Performance of cardiac troponins within the HEART score in predicting major adverse cardiac events at the emergency department. Am J Emerg Med. 2019 Aug 30.[34]

Summary: This prospective, single-center, observational cohort study evaluated the performance of a modified HEART score plus a single cTn using three different cTn assays to predict 30-day MACE in 1,002 patients. The sensitivities of modified HEART score plus Roche hs-cTnT (using "normal" of 14 vs 30 ng/L) Abbott hs-cTnI, and Beckman c-cTnI ranged from 84.9% to 87.0%.

Conclusion: HEART score calculated with three different cTn assays (and two cutpoints for hs-cTnT) had similar but insufficient sensitivity for ruling out 30-day MACE.

Low-risk patients: Modified HEART score.

Limitations: This study was conducted at a single hospital in Singapore. The study used a broad definition of MACE that included AMI, unstable angina, stroke, all-cause mortality, PCI, and CABG.

I. Wang, *et al.* Comparison of usual care and the HEART score for effectively and safely discharging patients with low-risk chest pain in the emergency department: would the score always help? Clin Cardiol. 2020 Apr;43(4):371-378.[35]

Summary: This single-center, prospective, observational study compared usual care to HEART score ≤3 for identifying low-risk ED patients for discharge in 2,185 patients with symptoms of ACS within 24 hours, defined as physician ordering cTn. The MACE rate for patients discharged under usual care was 2.2% (20/926); sensitivity 96.7%. The 30-day MACE rate would have been 5.2% (27/524) for HEART ≤3; sensitivity 95.6%.

Conclusion: Usual care and HEART score had similar sensitivity for 30-day MACE, and usual care safely identified more patients for discharge from the ED.

Low-risk patients: HEART score ≤3

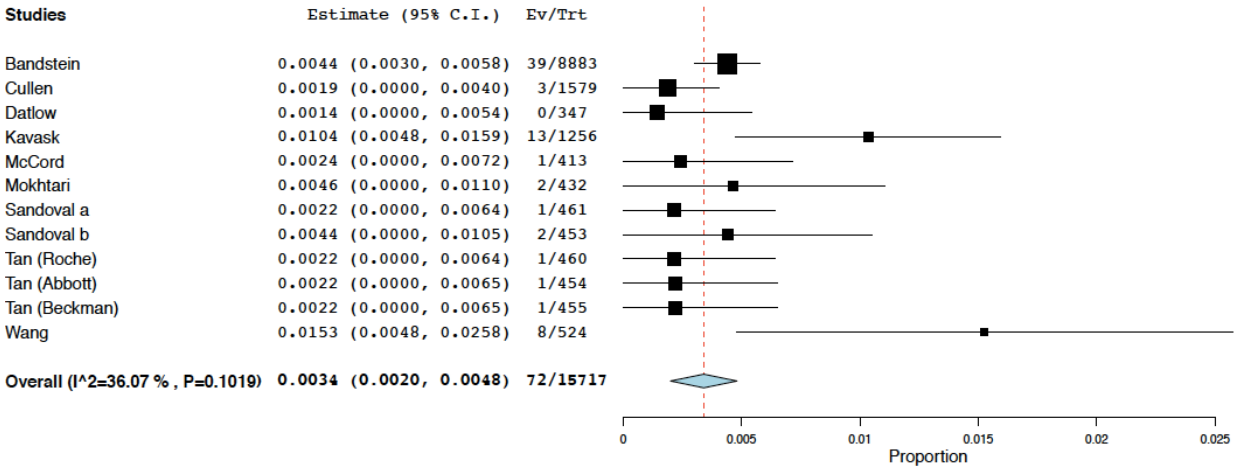
Limitations: This study was conducted at a single hospital in China with high rate of discharge with usual care. It is unclear whether clinical suspicion was so low that HEART should not have been applied or whether management of acute chest pain differs between China and US. The study also used HEART score rather than HEART

pathway (modified HEART + negative trops); HEART pathway was only applied in the minority of patients (n=340) who received serial troponins.

I. Forest Plots/Summary – n/a

Because there was no systematic review on the topic, but enough articles were retrieved with indirect evidence, the methods team used OpenMeta software for meta-analyses following a random-effects model as described by DerSimonian-Laird. We estimated the incidence per 1,000 patients with 95% CI. When the number of events was zero, we calculated the CI using the modified Wald method.

Pooled incidence is 3.4 per 1,000 patients (95%CI 2.0 to 4.8 per 1,000)



II. Summary of Evidence

Study	Total Patients	Low-Risk Patients	Low-risk Definition	Assay/Threshold	Overall Quality	Low-risk pt with 30 days AMI or MACE

Bandstein[27]	16,636	8,883*	Nonischemic ECG	hs-cTnT <5 ng/L	High	39/8883
Cullen[28]	1,635 / 909	1,308 / 659	TIMI 0	hs-cTnI <26.2 ng/L	Moderate	3/1579
Datlow[29]	888	333 (242 low-risk) / 143 (105 low-risk)	mHEART ≤3; ACS PPA <2%	cTnI <0.01 ng/mL	Low	0/347
Kavask[30]	4,425	TnT 444 / TnI 378*	CCS 0	hs-cTnT <8 ng/L hs-cTnI <4 ng/L	Low	13/1256
McCord[31]	1,282	413†	mHEART ≤3	hs-cTnT <14 ng/L	Moderate	1/413
Mokhtari[32]	1,020	432‡	TIMI ≤1 and nonischemic ECG	hs-cTnT <5 ng/L	Moderate	2/432
Sandoval[33]	2,212	46%	Nonischemic ECG	hs-cTnI <5 ng/L	Moderate	1/461 and 2/453
Tan[34]	1,002	460 / 483 / 454/ 455*	mHEART ≤3	hs-cTnT <14 ng/L hs-cTnT<30 ng/L hs-cTnI: Female <15 ng/L; Male <34 ng/L cTnI <30 ng/L	Low	Roche 1/460 Abbott 1/454 Beckman 1/455
Wang[35]	2,185	524	HEART ≤3	N/R; 99th percentile	Low	8/524 (death, MI, revasc)

*Includes only patients with a troponin below the listed threshold.

†Includes only patients with initial and second troponin below the listed threshold.

‡Includes only patients with troponins ruled out by 0/1 hour ADP

Appendix 3: Evidence Retrieval, Assessment, and Synthesis for Question 2

Question 2- (P) In adult patients with recurrent, low-risk chest pain, and negative or non-diagnostic stress testing within the last 12 months, (I) does repeat provocative stress testing vs (C) no stress test have an effect on (O) MACE within 30 days? [modified for each specific stress test: treadmill testing, echo and nuclear/perfusion stress test]

Previously: (P) In adult patients with recurrent, low-risk chest pain, (I) is repeated provocative stress testing within 12 months vs (C) no stress test for (O) MACE within 30 days? [modified for each specific stress test: treadmill testing, echo and nuclear/perfusion stress test]

1. Evidence Retrieval, Assessment and Synthesis

Included Studies: A total of 5,252 titles were reviewed, 334 articles selected for full text review, 35 studies (21+14) were included for PICO#8, and 3 that were indirectly relevant to the PICO question and thus were selected to create this recommendation.

I. **Lim SH, Anantharaman V, Sundram F, Chan ES, Ang ES, Yo SL, Jacob E, Goh A, Tan SB, Chua T. Stress myocardial perfusion imaging for the evaluation and triage of chest pain in the emergency department: a randomized controlled trial. *J Nucl Cardiol.* 2013 Dec;20(6):1002-12.[40]**

a. **Summary:** This is a randomized controlled trial which evaluated whether adding stress myocardial perfusion imaging (SMPI) to an evaluation strategy for emergency department (ED) patients presenting with chest pain more effectively identifies patients with ACS. Participants were adults aged 25 years and older presenting to a single ED with acute chest pain who had ruled out for AMI after 6 hours. High risk patients were excluded (known CAD, heart failure,

unstable angina). Patients were randomized 2:1 to stress myocardial perfusion imaging (SMPI) test within 24 hours or standard clinical assessment. Participants with normal stress scans were discharged from the ED with a cardiology outpatient appointment within 2 weeks. Participants with abnormal stress scans were admitted. Primary outcome was cardiac event at 30 days (cardiac death, MI, VF, APE requiring RSI, cardiogenic shock). Secondary outcome was significant CAD on coronary angiogram, PCI, or CABG.

   i. **SMPI group:** 1,004 patients. **Control group:** 504 patients.
   ii. There were no statistically significant differences in the risk of cardiac events, significant CAD, or cardiac death between the two groups.

b. **Conclusion:** This study suggests that stress myocardial perfusion imaging for patients with acute CP and no MI does not decrease rates of cardiac events at 30 days.

c. **Limitations:** Participants were excluded if they had previous angiogram or SMPI/echo in last 18 months. Participants were not necessarily low risk by HEART score or other risk-stratification tool, and chest pain was not necessarily "recurrent". Patients did not necessarily have recent provocative testing.

Table 2. Clinical Outcomes at 30 days

Outcome	SMPI n=1004	Standard Care, n=504	RR (95% CI)
Cardiac Death	0	0	n/a
Cardiac Event	4 (0.4%)	4 (0.79%)	0.5 (0.13-2.00)
Significant CAD	36 (3.59%)	15 (3.00%)	1.2 (0.61-2.17)
Total:	40 (3.98%)	19 (3.77%)	

II. **Frisoli TM, Nowak R, Evans KL, Harrison M, Alani M, Varghese S, Rahman M, Noll S, Flannery KR, Michaels A, Tabaku M, Jacobsen G, McCord J. Henry Ford HEART Score Randomized Trial: Rapid Discharge of Patients Evaluated for Possible Myocardial Infarction. Circ Cardiovasc Qual Outcomes. 2017 Oct;10.[39]**

a. **Summary:** This is a randomized controlled trial of ED patients being evaluated for AMI who were low risk, defined as a modified HEART score of 3 or less (with 2 troponins at 0 and 3 hours). Subjects were randomized 1:1 to immediate discharge (n=53) versus management in an observation unit with stress testing (n=52). The primary end points were 30-day total charges and length of stay. Secondary end points were all-cause death, nonfatal AMI, rehospitalization for evaluation of possible AMI, and coronary revascularization at 30 days. There were no deaths, AMIs, or coronary revascularizations in either group. LOS and healthcare costs were lower in the early discharge group.

    i. Of the 42 patients who had a stress test, 1 (2%) patient had an abnormal stress test. Was later deemed to be artifact upon follow-up with cardiology and did not undergo further testing.

b. **Conclusion:** This study suggests among ED patients with chest pain with a modified HEART score of 3 or less, stress testing does not decrease cardiac events at 30 days.

c. **Limitations:** Chest pain was not necessarily recurrent. Relatively small sample size. No power calculation was done. Primary outpoint was cost. Patients did not necessarily have recent provocative testing.

III. **Natsui S, Sun BC, Shen E, Wu YL, Redberg RF, Lee MS, Ferencik M, Zheng C3, Kawatkar AA, Gould MK, Sharp AL. Evaluation of Outpatient Cardiac Stress Testing After Emergency Department Encounters for Suspected Acute Coronary Syndrome. Ann Emerg Med. 2019 Aug;74(2):216-223.[41]**

a. **Summary:** This was a multicenter, retrospective analysis of ED encounters of patients with chest pain diagnosis being considered for outpatient stress testing. The primary outcome was the proportion of patients who completed an outpatient stress test within the recommended 3 days, 4 to 30 days, or not at all. Secondary analysis described the 30-day incidence of major adverse cardiac events.

    a. **Total sample size:** 7,988 patients. 2,497 completed the stress test within 72 hours, 4,695 did so with 4-30 days, and 796 did not complete stress testing within 30 days. Combination of stress ECG, stress Echo, and MPI.

    b. **Outcomes:** There were no all-cause deaths within 30 days. The rates of other types of 30-day major adverse cardiac events were low, with acute myocardial infarction at 0.7% and revascularization by percutaneous coronary intervention or coronary artery bypass grafting at 0.3%. Rapid receipt of stress testing was not associated with lower adverse outcomes (Table 3) because patients completing stress testing within 72 hours were as likely to experience 30-day major adverse cardiac events as those who did not (odds ratio 0.92; 95% confidence interval 0.55 to

1.54). Subgroup analysis of 2,151 encounters with documented HEART scores (1,560 low risk, 584 moderate risk, and 7 high risk) showed that different risk pools did not affect the timing of follow-up stress testing.

b. **Conclusion:** There does not appear to be any associated benefit of stress testing within 3 days, nor within 30 days, compared with never receiving testing at all.

c. **Limitations:** Non-randomized study creates risk of unmeasured confounders. Patients who completed a stress test before discharge were excluded. All HEART scores were included, 72.5% were HEART 0-3. Chest pain was not necessarily recurrent. Patients did not necessarily have recent provocative testing.

Table 3. 30-day major adverse cardiac outcomes stratified by timing of noninvasive cardiac stress test completion after an ED visit for suspected acute coronary syndrome.

Outcome	Noninvasive Test Completion Timeframe			
	Within 3 Days (N=2,497)	4 to 30 Days (N=4,695)	None Within 30 Days (N=796)	Total (N=7,988)
Death, N	0	0	0	0
AMI, No. (%)	19 (0.8)	30 (0.6)	5 (0.6)	54 (0.7)
PCI, No. (%)	2 (0.1)	2 (<0.1)	0	4 (0.1)
CABG, No. (%)	6 (0.2)	7 (0.1)	0	13 (0.2)
Unstable angina, No. (%)	18 (0.7)	24 (0.5)	1 (0.1)	43 (0.5)
MACE, No. (%)	27 (1.1)	39 (0.8)	5 (0.6)	71 (0.9)

AMI, Acute myocardial infarction; *PCI*, percutaneous coronary intervention; *CABG*, coronary artery bypass grafting; *MACE*, major adverse cardiac events (includes death, AMI, PCI, and CABG).

3. Summary Effect Tables

Table 3. Stress testing for ED patients with recurrent, low-risk chest pain.

Outcome	Number of subjects (intervention)	Number of Subjects (controls)	Results for intervention	Results for control	Absolute risk per 1000	Number Needed to Treat	Standardized mean difference (95% CI)
Death (All 3 studies)	1004+52+2497 = 1305	504+53+796 = 636	0+0+0 = 0	0+0+0 = 0	0	n/a	n/a
Cardiac Event (Lim)	1004	504	4 (0.39%)	4 (0.79%)	0.79%-0.39% = 0.4%	250	
Significant CAD (Lim)	1004	504	36 (3.59%)	15 (3.00%)	3%-3.59% = -0.59	n/a	
MACE (Frisoli and Natsui)	52+2497 = 2549	53+796 = 849	0+27 = 27 27/2549 = 1.06%	0+5 = 5 5/849 = 0.59%	0.59% - 1.06% = -0.47%	n/a	

4. Risk of Bias

Table 4. Risk of Bias for Lim et al. and Frisoli et al.

Author/ Year	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting
Lim 2013	L	L	H	U	U	L
Frisoli 2017	L	L	H	U	L	L

L, low risk; U, unclear risk; H, high risk

Table 5. Risk of Bias for Natsui et al. (ROBINS-1 for non-randomized studies of interventions)

Domain	Explanation	Risk of Bias
Pre-intervention	**Risk of bias assessment is mainly distinct from assessments of randomized trials**	**Low risk, Moderate risk, Serious risk or Critical risk**
Bias due to confounding	Baseline confounding occurs when one or more prognostic variables (factors that predict the outcome of interest) also predicts the intervention received at baseline	Moderate
Bias in selection of participants into the study	When exclusion of some eligible participants, or the initial follow-up time of some participants, or some outcome events is related to both intervention and outcome, there will be an association between interventions and outcome even if the effects of the interventions are identical. This form of selection bias is distinct from confounding—A specific example is bias due to the inclusion of prevalent users, rather than new users, of an intervention	Low
At intervention	**Risk of bias assessment is mainly distinct from assessments of randomized trials**	
Bias in classification of interventions	Bias introduced by either differential or non-differential misclassification of intervention status. Non-differential misclassification is unrelated to the outcome and will usually bias the estimated effect of intervention towards the null.	Low

Domain	Explanation	Risk of Bias
	Differential misclassification occurs when misclassification of intervention status is related to the outcome or the risk of the outcome, and is likely to lead to bias.	
Post-intervention	**Risk of bias assessment has substantial overlap with assessments of randomized trials**	
Bias due to deviations from intended interventions	Bias that arises when there are systematic differences between experimental intervention and comparator groups in the care provided, which represent a deviation from the intended intervention(s) Assessment of bias in this domain will depend on the type of effect of interest (either the effect of assignment to intervention or the effect of starting and adhering to intervention).	High
Bias due to missing data	Bias that arises when later follow-up is missing for individuals initially included and followed (such as differential loss to follow-up that is affected by prognostic factors); bias due to exclusion of individuals with missing information about intervention status or other variables such as confounders	Moderate
Bias in measurement of outcomes	Bias introduced by either differential or non-differential errors in measurement of outcome data. Such bias can arise when outcome assessors are aware of intervention status, if different methods are used to assess outcomes in different intervention groups, or if measurement errors are related to intervention status or effects.	Low
Bias in selection of the reported result	Selective reporting of results in a way that depends on the findings and prevents the estimate from being included in a meta-analysis (or other synthesis)	Low

5. Summary of Evidence

Comparison	Outcome	Study design (# studies)	Findings	Evidence type *	Overall evidence type
Same-visit stress testing vs Control	Death	2 RCTs	No difference	Class II	Class III
	Cardiac Event and Significant CAD	1 RCT	No difference	Class II	
	MACE	1 RCT	No difference	Class II	
3-day stress testing vs none	MACE	1 (non-randomized interventional)	No difference	Class III	

*Evidence type based on Sackett DL et al. classification, 1989.

6. Moving from Evidence to Recommendation

Overall evidence type across all *critical* outcomes	2

Outcome	Values and Preferences
MACE	High value
Death	High value
Significant CAD	Moderate value

Appendix 4: Evidence Retrieval, Assessment, and Synthesis for Questions 4 and 5

Question 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?

Question 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?

1. Evidence Retrieval, Assessment and Synthesis

Included Studies: A total of 5,252 titles were reviewed, 334 articles selected for full text review. While none of the sources directly address recurrent, low-risk chest pain, there are several sources that provide an evidence base for negative cardiac catheterization and risk of subsequent ACS and time to ACS including 1 systematic review and meta-analysis:

a. Radico F, Zimarino M, Fulgenzi F, et al. Determinants of long-term clinical outcomes in patients with angina but without obstructive coronary artery disease: a systematic review and meta-analysis. Eur Heart J. 2018;39(23):2135-2146. doi:10.1093/eurheartj/ehy185[59]

Summary: This is a systematic review and meta-analysis which evaluated the composite primary outcome of all cause death and nonfatal MI using a random effects models to estimate pooled incidence in patients with angina without obstructive CAD. The authors included 54 studies, reporting outcomes in 35,039 patients (mean age 56, male/female ratio 0.51, 99,770 person-years) with angina and no obstructive CAD. After a median follow-up of 5 years (interquartile range 3-7 years), the pooled incidence of the primary outcome was

0.98/100 person-years [95% confidence interval (CI) 0.77-1.19%], with considerable heterogeneity among studies (I2 = 91%, P < 0.001). The primary outcome was associated with prevalent dyslipidaemia (P = 0.016), diabetes (P = 0.035), and hypertension (P = 0.016). Studies enrolling patients with less-than-obstructive CAD showed a higher incidence of the primary outcome (1.32/100 person-years, 95% CI 1.02-1.62) compared with studies including only patients with 'entirely normal' coronary arteries (0.52/100 person-years, 95% CI 0.34-0.79, respectively; P < 0.01). We excluded studies using CTA instead of catheterization, thus in all 39 studies included. 24 studies that had outcomes for those with 0% stenosis and 20 studies with outcomes for 1-49% or unspecified non obstructive stenosis.

Conclusion: This review shows the low incidence rate of death and nonfatal MI among patients with both nonobstructive and no CAD.

Limitations: The authors included both studies using diagnostic angiograms as well as coronary CT angiograms, and excluded studies with follow up less than one year. Again, there little documentation of patient risk stratification.

b. Michael N. Papanicolaou, Robert M. Califf, Mark A. Hlatky, Ray A. McKinnis, Frank E. Harrell, Daniel B. Mark, Bernie McCants, Robert A. Rosati, Kerry L. Lee, David B. Pryor. Prognostic implications of angiographically normal and insignificantly narrowed coronary arteries. The American Journal of Cardiology. Volume 58, Issue 13, 1986, Pages 1181-1187. https://doi.org/10.1016/0002-9149(86)90378-4.[61]

Summary: This is a single center retrospective study that followed up patients after cardiac catheterizations for suspected ischemic heart disease. 1,491 of 7,317 patients had

arteriograms interpreted as showing normal vessels or minor irregularities (less than 25% luminal diameter narrowing). All patients were followed by clinic visits, mailed questionnaires, or telephone interviews at 6 and 12 months and annually thereafter. A definite nonfatal myocardial infarction was diagnosed when the infarction was documented by all 3 of the following criteria: a new Q wave on the standard electrocardiogram; elevation of the MB fraction of creatine kinase or reversal of the normal lactic dehydrogenase-1 to lactic dehydrogenase-2 ratio: and symptoms compatible with AMI. Those with normal cath were a median of 47 years old, 42% male. Those with insignificantly narrowed or normal coronary arteries had a 99% survival at 5 years and over 98% survival at 10 years. In addition, the Kaplan-Meier estimates of infarction-free survival at 1, 5 and 10 years were 100%, 99% and 98% for patients with normal coronary arteries. Chest discomfort was still present in 70% of all patients and was equally prevalent in patients with normal and insignificantly diseased coronary arteries.

Conclusion: Patients with normal and insignificantly narrowed coronary arteries have low rates of cardiac death and nonfatal myocardial infarction.

Limitations: The study evaluated patients with angiographies done between 1969-1983, and the definition of acute coronary syndrome has changed significantly since then. Not specific to ED patients; arguably not low-risk chest pain because underwent catheterization but recurrent symptoms because median baseline duration of symptoms between 13 and 21 months depending upon group. Survival/Kaplan Meier curves presented but difficult to determine absolute numbers without censoring data.

c. William R. Pitts, Richard A. Lange, Joaquin E. Cigarroa, L.David Hillis. Repeat coronary angiography in patients with chest pain and previously normal coronary angiogram, The American Journal of Cardiology. Volume 80, Issue 8, 1997, Pages 1086-1087. https://doi.org/10.1016/S0002-9149(97)00610-3. (http://www.sciencedirect.com/science/article/pii/S0002914997006103)[64]

Summary: This is a retrospective single center study in which the authors reviewed 17 patients (case series) with a previously normal angiography and had repeat angiography for chest pain. The patients were between 43-72 years old (mean 55), with risk factors of hypertension, diabetes, tobacco use. The time between repeat coronary angiography was on average 8.9 +/- 3.3 years. During this time, 2 patients developed single vessel CAD and one had MI (both within 5 years).

Conclusion: Patients with chest pain and normal angiography have low risk of MI.

Limitations: Brief report vs Letter. Retrospective looking specifically for subjects with previously normal cath reports in the cohort. This is a single center small study, which evaluated patients with angiographies done between 1970-1997, and the definition of acute coronary syndrome has changed significantly since then.

d. McMullan JT, Lindsell CJ, Blomkalns AL. Five-year mortality and coronary heart disease development after normal coronary angiogram. *World J Emerg Med*. 2011;2(1):24-29. doi:10.5847/wjem.j.1920-8642.2011.01.004[60]

Summary: This is a single center retrospective chart review of patients who had normal angiography. Normal is defined as absence of any abnormality. Patients had cardiac

catheterization performed between January-May 2009. During this time 129 of 582 (22%) were found to have normal angiograms. Charts were abstracted for development of coronary heart disease based on repeat angiography, need for revascularization, and all-cause mortality. Observed all-cause mortality was 10.1% (13/129, 95 CI 5.7% to 16.9%). Among those who died, median survival was 106 weeks (0 to 246 weeks). Causes of death were cardiac in 3 patients, multi-organ system failure in 2, ischemic stroke in 1, malignancy in 1, and unknown in 6 (determined by SSDI review). There were 15 patients who underwent repeat angiography. New angiographic lesions were found in 6 patients between 2 to 5 years after initial angiogram. One patient underwent percutaneous coronary intervention.

Conclusion: In this cohort of patients, 11% of patients had repeat angiogram within 5 years and of these, 40% had newly identified coronary artery disease.

Limitations: Only 70 of 129 patients had complete medical records for review at 5 years; and records were not obtained for patients who may have received care outside of this single center.

e. Wang, T.K.M., Oh, T.H.T., Samaranayake, C.B., Webster, M.W.I., Stewart, J.T., Watson, T., Ellis, C. and Ruygrok, P.N. (2015), The utility of a 'non-significant' coronary angiogram. Int J Clin Pract, 69: 1465-1472. doi:10.1111/ijcp.12723[63]

Summary: Cases of coronary angiography at a single center in Auckland, New Zealand from January 2010-April 2011 (15 months) were reviewed. Of 2983 cases, 366 underwent coronary angiography for evaluation of chest pain and were found to have absent or mild CAD (defined as <50% stenosis). These patients were followed up for 2.3 +/-0.6 years.

Mean age was 60.0 +/- 12.3 years, 56.1% were female. Rates of major adverse cardiovascular events and readmissions with chest pain were 0.3% (1) and 1.9% (7) respectively at 30 days, and 1.9% (7) and 6.0% (22) at 1 year. During the complete "long term follow up" period (out through January 2013; between 22 – 36 months depending upon when the subject was enrolled in the study period) showed rates of major adverse cardiovascular events and readmissions with chest pain were 4.1% (15) and 9.8% (36) respectively.

Conclusion: There is a small risk of ACS even with a normal cardiac catheterization within 2 years. Those with mild CAD have a higher risk than those without.

Limitations: Single center study completed in New Zealand; these were not referrals from the ED. Unclear if this is low risk group.

f. Tavella R, Cutri N, Tucker G, Adams R, Spertus J, Beltrame JF. Natural history of patients with insignificant coronary artery disease. Eur Heart J Qual Care Clin Outcomes. 2016;2(2):117-124. doi:10.1093/ehjqcco/qcv034[62]

Summary: Cases of elective coronary angiography for chest pain at two Adelaide, Australia hospitals between 2003-2007. Results were classified as CAD (coronary stenosis ≥50%) or insignificant CAD (<50%). These patients were also compared against a "healthy control cohort" of a population-based study that did not report history of heart attack or angina. Of 758 patients, 253 (33%) had insignificant CAD. These patients were younger, more predominantly female and less likely to have traditional cardiac risk factors. (mean age 58 +/- 12 vs 63 +/- 10, 57% female vs 28%). In one year follow up, there was one non-fatal MI and no deaths in those with insignificant CAD. In addition, there was a 4% ED

repeat chest pain presentation, and 3% were readmitted. About half of the patients still experienced chest pain.

Conclusion: While those with insignificant CAD have better one-year prognosis than those with CAD, they had persistent chest pain and had QOL more similar to those with CAD than those without.

Limitations: this is again, elective angiography patients, and QOL data only on 70% of patients.

Table 1. Studies included in Radico et al[59] meta-analysis.

Author/ Year/Funding	Methods/ Participants	Intervention	Main outcomes	Notes
Addison 2014[97] **n/a funding**	Retrospective chart review	47 patients with chest pain, abnormal nuclear stress test, and <40% luminal narrowing on angiography	combined endpoint of definite or suspected death from heart disease (including sudden cardiac death), non-fatal myocardial infarction and fatal or non-fatal stroke with mean duration of follow-up was 19.1 ± 8.4 months (range 9-47 months), which yielded a total of 898 patient-months of follow-up, 53% (26) of patients had combined outcome. 22 (46.8%) patients had recurrent chest pain necessitating emergency room	Single site Unable to tease out singular outcomes
Bugiardini 2004[98] **Funding n/a**	Prospective enrollment of 42 women with chest pain, 37 patients with repeat angiogram in 10 years.	Follow up for 10 years	1 patient with AMI and death, 13 patients with persistent chest pain, 13/17 patients developed stenosis on repeat angiography	
Cortigiani 2014[99]	Prospective cohort of 144 patients with DM and no or non-obstructive CAD on angiography (no breakdown).	median follow-up period of 29 months (interquartile range, 14–44 months),	17 hard events (five deaths, 12 nonfatal myocardial infarctions) were registered.	

Delcour 2009[100] **Funding unknown**	Retrospective case series 48 patients who reversible perfusion and normal coronary arteries	Follow up for at least 3 years (mean 7.4)	Study endpoints were cardiovascular events defined as sudden cardiac death, myocardial infarction, percutaneous coronary revascularization, coronary artery bypass grafting, and cerebrovascular or peripheral revascularization. 31% (15/48) of the patients had cardiovascular events.6/48 patients had coronary events. The time between myocardial perfusion imaging and coronary event was 0.5 to 8.67 years.	Excluded known lv dysfunction, and known cad, cardiomyopathy
Egashira 1987[101] **Funding unknown**	Retrospective study of 90 patients with vasospastic angina	Followed for mean 4 years	1 patient with MI in 8 months 2 sudden deaths (2nd and 3rd year of follow up)	Methods minimal for follow-up
Foussas 1998[102] **Funding unknown**	Retrospective study with 160 patients with chest pain with normal coronary angiograms (<25% luminal irregularities)	followed for mean 2.5 years	During follow up 95 patients (59%) continued to have chest pain. 1 patient with sudden cardiac death and two patients had a nonfatal MI	
Gulati 2009[103] NLBI, National Center for Research Reousrces, Gustavus and Louis Pfeiffer Research Foundation, Women's Guilde of Cedars Sinai Medical Center, Ladies Hospital Aid Society of Western Pennsylvania	Prospective 540 women with coronary angiograms	Followed for mean 5.2 years	Primary Composite 5-year rate of nonfatal MI, hospitalization for CHF, stroke, or cardiovascular death. Those of 0% stenosis 0.9% MI, 1.5% death due to CV, 3% all-cause mortality <49% stenosis 3.9% MI, 4.4% death due to CV, 8.2% all cause mortality	
Halcox 2002[104] **Funding unknown**	176 patients with angiographically smooth coronary arteries on cath.	Mean duration of follow-up was 46.3±2.7 months	2 sudden cardiac deaths, 5 MI, 5 unstable angina, 1 CVA, 3 PCI, 2 CABG	

		(median 40.7 months).		
Humphries 2008[105] BC provincial Health Services Authority provided data. GENESIS, an Interdisciplinary Collaboration Enhancement Team supported by the Canadian Institutes for Health Research and the Heart and Stroke Foundation of Canada, funded this project	retrospective review of cardiac catheterizations performed in British Columbia from 7/1/1999 to 12/31/2002 3647 patients with normal coronaries	Followed for one year	Within 1 year of catheterization, 1.0% died (19 women, 18 men, P = .27), 0.6% had a stroke (13 women, 9 men, P = .91), and 0.1% underwent revascularization (3 women, 2 men, P = .87). 30 (1.4 %) women were rehospitalized for chest pain with repeat cardiac catheterization vs 7 men (0.5%); 19/30 F vs 3/7 M were within 180 d. 9/30 recath: 4 normal, 3 with 1 vessel <50%, 2 with >75% 2/7 M recath normal.	Most of cases were for stsable angina 6% had prior MI
Isner 1981[106] **Funding unknown**	Retrospective analysis of 121 patients who underwent cath (normal - 109 (90%); <50% in remaining 12.	Mean length of follow-up was 4.3 years (range 1 to 11 years).	3 (2.5%) patients died 53, 60, and 48 months, following catheterization. 4 nonfatal MI 2 included folks had MI prior to inclusion.	
Jespersen 2011[107] This work was supported by The Danish Heart Foundation (09-10-R75-A2682-22569).	Retrospective cohort study of all patients in Eastern Denmark having CAG performed for the first time with suspected stable angina. 5183 patients (3479 with normal caths and 1704 with diffuse non-obstructive CAD (defined as 1–49% stenosis in any epicardial coronary artery). Reference population: 5695 age-stratified	The median and maximum follow-up time were 4.6 and 11.1 years, respectively (inter-quartile range 2.0–6.9 years). The primary composite endpoint consisted of major adverse cardiovascular events (MACE), defined as cardiovascular mortality, hospitalization	The primary MACE outcome (cardiovascular mortality, hospitalization for MI, heart failure, or stroke) occurred in 1351 men and 837 women. Pooling analyses of men and women yielded HRs for angina with normal coronary arteries of 1.52 (1.27–1.83, P <0.001) and for diffuse non-obstructive CAD of 1.85 (1.51–2.28, P< 0.001) (multivariable-adjusted model). The increased risk of MACE in symptomatic patients with normal coronary	MACE events are pooled thus we don't have absolute values for each outcome of interest and outcomes that we weren't following (CVA) are included.

	sample of men and women, aged 20 years or more, randomly selected from a defined area of Copenhagen, Denmark.	for MI, heart failure, or stroke.	arteries or diffuse non-obstructive CAD was largely accounted for by increased rates of cardiovascular death and either hospitalization with heart failure or MI. The 5-year MACE-free survival probabilities were 0.98, 0.94, 0.92, in women and 0.94, 0.89, 0.86, in men for the reference population, patients with normal coronary arteries, diffuse nonobstructive CAD, respectively.	
Kaski 1995[108] **Funding Unknown**	Prospective analysis of 99 patients with cardiac syndrome X and normal coronary arteriograms in the absence of coronary artery spasm		During follow-up, no deaths or myocardial infarctions occurred	
Lamendola 2010[109] **Funding Unknown**	155 patients with cardiac syndrome X and completely normal epicardial coronary arteries at angiography	Follow-up time was on average 137±78 months (range 24 to 372)	No patient died from cardiovascular causes neither developed a non-fatal AMI. Repeat cath in 33 (21.3%). One had mild atherosclerotic coronary artery disease; revascularizaiton in 2 patients (1.3%)	
Leu 2005[110] **Funding Unknown**	92 consecutive patients with normal coronary angiograms	Clinical follow-up was completed in all patients for a mean period of 31.5± 14.2 months (range 38–1776 days).	No death, MI, revascularization 8 readmitted for ACS but repeat evaluation showed normal coronary angiograms in all of these patients	
Li 2012[111] **Funding Unknown**	80 consecutive patients with chest pain and normal coronary arteries	Patients were followed up for 6 months	no deaths, myocardial infarction or revascularization procedures	Randomized to diltiazem vs placebo to observe the effect on patients with coronary

	evidenced by coronary angiography and CSF were included in this randomized, double-blind, placebo-controlled trial			slow flow (CSF) phenomenon.
Lichtlen 1995[112] **Funding Unknown**	Retrospective analysis of 176 patients with normal coronary and left ventricular angiographic findings	Follow up median interval of 148.5 months (range 70 to 190months). Of the 176 patients, 93 (53%) had been followed up for >12 years, 38 (22%) for <10 years.	12 patients died during follow-up, 4 from cardiac causes. The total mortality rate was 6.8% (0.55%/year), cardiac mortality rate 2.3% and coronary mortality rate 1.14% (0.09%/year) 4 nonfatal MI occurred 33 to 140 months after initial angiography	
Lim 2016[113] **Funding Unknown**	Prospective analysis of 777 patients vasospastic angina with <50% stenosis on cath stratified by aspirin use.	follow-up period of 52.1 months	19 all cause death, 7 cardiac deaths, 11 non-fatal MI, 9 revascularizations	
Marks 2004[114] Funding Unknown	Retrospective study 168 patients with normal caths undergoing coronary flow evaluation	Follow-up was performed at a mean of 8.5±1.6 years in the abnormal CFR groups and 8.4±2.1 years in the normal CFR group.	All-cause mortality 20 deaths	All-cause mortality only. No evaluation of MI or cardiac related death.
Masumoto 2001[115]	Prospective analysis 68	3.3 years (range 1.0–5.5)	0 deaths 3 nonfatal MI	

Supported by grants from the Japanese Ministry of Education, Science, and Culture, Tokyo, Japan.	patients with microvascular angina microvascular spasm and <50% stenosis on cath.			
Nitenberg 2004[116] Funding Unknown	56 control subjects and 72 type 2 diabetic patients with normal coronary arteriography	The mean follow-up was 45 ±19 months (range 27–68).	0 deaths, MIs in control group. 1 sudden cardiac death, 3 MI, 4 angioplasties, 2 revascularizations in diabetic group	
Nitenberg 2005[117] Funding Unknown	124 patients (65 nondiabetic hypertensive and 59 normotensive type 2 diabetic) patients with normal coronary arteriography	mean follow-up was 112±9 months (range 88–124 months),	1 sudden cardiac death, 3 MI, 5 angioplasties, 4 revascularization.	Hypertensive vs diabetic patients
Pasternak 1980[118] Funding Unknown	175 patients with chest pain and documented arteriographically normal coronary arteries or minimal coronary disease (less than or equal to 30% luminal narrowing).	information was available in 159 patients over a mean follow-up period of 42.7 months.	There were no deaths, and only one myocardial infarction occurred during this period.	
Proudfit 1980[119] Funding Unknown	521 patients whose coronary arteriograms did not show any severe obstruction. 357 with normal cath 101 with moderate (<30%) 63 with (30-50%)	All were followed for 10 years or until death.	Gross survival at 10 years for the group with normal arteriograms or mild lesions was 93.6% and survival from coronary disease was 99.2%. Gross survival for the 63 patients who had moderate lesions was 74.6% at 10 years and survival from coronary disease was 83.5% Normal cath group – 2 deaths, 2 nonfatal infarcts; <30% group – 2	

			deaths, 8 nonfatal infarcts; 30-50% group - 10 deaths, 4 nonfatal infarcts	
Sakata 2005[120] Funding Unknown	examined 105 subjects who were referred for cardiac catheterization and were found to have nearly normal coronary arteries without spasm and normal cardiac function	The median follow-up period was 4.7 years with a range of 1–7 years.	1 patient died suddenly and another died of acute MI. Two patients developed nonfatal acute MI and 7 patients underwent emergency coronary angiography because of unstable angina.	No pt lost to follow-up.
Sanchez-Recalde 2009[121] Funding Unknown	147 consecutive patients with angina and normal coronary arteries on coronary angiography	mean follow-up of 7 years	only 6 patients had major cardiac events excluding hospitalizations for angina	Pulled from abstract as I cant find the full manuscript.
Schindler 2003[122] supported by a grant from the German Research Foundation (So 241/2-2) and from the government of Baden-Württemberg	Prospective study of 130 patients with normal coronary angiograms as defined by the absence of angiographic evidence for coronary artery disease were studied prospectively.	mean duration of follow-up was 45±9 months.	total of 26 of 130 (20%) patients experienced at least 1 cardiovascular event. 1 sudden death, 13 Acute coronary syndromes, 5 nonfatal Mis, 14 angioplasties, 1 CABG.	
Schofield 1990[123] Funding none	Prospective Study of 63 consecutive patients who presented with typical angina pectoris and who were found to have completely normal coronary angiograms.	Mean follow-up six to twenty-four (mean 14.9) months	No deaths	
Scholl 1988[124] Funding Unknown	48 consecutive patients with proved symptomatic coronary arterial	mean follow-up period was 47 ±22 months (range 12 to 85	4 mace events: 1 patient (2%) died of a cardiac-related cause.	Three patients had a previous myocardial infarction however none of

	spasm coronary angiography showing normal (n=10) or <50% narrowing (n=38).	months). Death.	MI occurred in 3 patients (6%).	them had an event during f/u.
Sedlak 2013[125]	Retrospective analysis of BC, Canada residents with stable angina, undergoing coronary angiography. 3087 patients enrolled (0% stenosis, n=2079; 1% to 49%, n=1008.	median follow-up time of 1.9 years and maximum follow-up of 3 years.	Within the first year, women with nonobstructive CAD had a higher risk of MACE than men with nonobstructive CAD (adjusted HR 2.43, 95% CI 1.08-5.49). Furthermore, women with nonobstructive CAD had a 2.55-fold higher risk of MACE than women with no CAD (95% CI 1.33-4.88). In contrast, men with nonobstructive CAD had a similar risk as men with no CAD (adjusted HR 0.61, 95% CI 0.26-1.45)	Absolute values of MACE events not provided in manuscript only hazard ratios Cardiac Services BC Registry (cardiac procedures and patient's clinical and demographic characteristics) with linkage to the BC Hospital Discharge Abstract Database (all hospitalization admissions) and BC Vital Statistics (all death records).
Shin 2012[126] Funding Unknown	Retrospective study using the data-sets of the VA-CMC (Vasospastic Angina in the Catholic Medical Center) registry. VSA patients with normal findings or minimal atherosclerotic stenosis (<50% of luminal diameter narrowing) on their baseline CAG were included in this study.	final analysis was performed in 745 patients (89.7%). The mean follow-up duration was 36.1±9.8 months.	19 patients died during the follow-up period (2.55%). Eleven patients died due to cardiac causes (1.48%, cardiac mortality rate). Of the patients who died from cardiac causes, 3 had acute fatal MI; 4 from severe heart failure; and 4 from sudden cardiac death. The mean duration from the VSA diagnosis to cardiac death was 10.6±4.3 months. 110 patients (14.8%) underwent repeat CAG, (15/745, 2.01%) underwent PCI for the development of significant atherosclerosis. The mean duration from the diagnosis to PCI was 27.5±9.9 months.	
Shin 2015[127] Funding Unknown	Prospective analysis of 2,129 patients in the VA-KOREA	The mean follow-up duration was	The 24-month incidences of cardiac death and acute coronary syndrome were	Only appears to have reported outcomes for positive and

	(Vasospastic Angina in KOREA registry of patients with All of the registered patients had normal findings or minimal (<50% luminal diameter narrowing) on cath who underwent intracoronary ergonovine provocation tests.	26.7 ± 8.8 months. Outcomes reported for 1100	(0.36%, 1.1% respectively) in the positive spasm and intermediate spasm groups. No outcome data provided for no spasm group. 12 MI, 4 cardiac death	intermediate spasm groups leaving out 690 patients. 1100 patients have data but the meta-analysis only reported on 432 – unclear why.
Shintani 2003[128] Funding Unknown	Retrospective analysis of 49 patients with syndrome X who met the following inclusion criteria; 1) angina-like chest pain, 2) ischemic ST-T change (≥1 mm ST-segment depression) on treadmill exercise tests, and 3) normal coronary arteriograms.	mean, 6.4 ± 3.8 years 44 with follow up data	The 5- and 10-year event free rates were 100% and 98%, respectively. one death due to cancer. One patient developed complete left bundle branch block after 5 years and one had complete atrioventricular block after 14 years. No other cardiac events, including myocardial infarction, were observed.	
Sicari 2005[129] institutional funding of the CNR, Institute of Clinical Physiology, Pisa, Italy	Retrospective analysis of 457 consecutive patients undergoing cath. 359 patients had completely normal, arteries; 45 had 'mild' (0–20%, mean 10±8% diameter stenosis) irregularities of at least one vessel; 50 had 'moderate' (20-40%, mean 31±8% diameter	median follow-up of 7.1 years (first quartile 5 and third quartile 10.5)	43 (10.6%) events (38 deaths of which 14 were attributed to cardiac causes and six myocardial infarctions) occurred.	Looks at prognostic value of dipyridamole echocardiography test (DET) and outcomes assessed in relation to results of DET not level of angiographic stenosis.

	stenosis) irregularities coronary angiography showing either absent or non-significant (<50% visually assessed) stenosis in any major vessel or secondary branch.			
Sicari 2009 [130] institutional funding by the CNR, Institute of Clinical Physiology, Pisa, Italy.	Retrospective analysis of 394 patients. 282 patients had completely normal, smooth coronary arteries; 28 had "mild" (0% to 20% diameter stenosis, mean 19 ± 2.6) irregularities of ≥1 vessel; 76 had "moderate" (20% to 40% diameter stenosis, mean 34 ±5) irregularities.	median follow-up of 51 months (first quartile 27, third quartile 74)	31 (7.8%) events (4 deaths and 27 nonfatal MIs [3 STEMIs and 24 NSTEMIs]) occurred.	Follow-up data were obtained from _1 of 4 sources: review of a patient's hospital record, personal communication with a patient's physician and review of a patient's chart, a telephone interview with a patient conducted by trained personnel, and/or a staff physician visiting a patient at regular intervals in the outpatient clinic.
Sullivan 1994[131] Funding Unknown	Retrospective analysis of 138 patients out of 896 referred to one cardiologist for cath over a 5 year period. Normal cath	Mean (SD) follow up time was 2.4 (1.4) years.	One myocardial infarction, 2 deaths from non-cardiac causes, and one sudden death of unknown cause.	Follow up details were obtained on 98% of patients.
Suwaidi 2000[132] Miami Heart Research Institute, Rappaport Vascular Biology Program, and	Prospective analysis of 168 consecutive patients with coronary artery lesions <40% lumen diameter stenosis without evidence of coronary spasm	followed up for a mean of 28 months (range, 11 to 52 months).	Over an average 28-month follow-up (range, 11 to 52 months), none of the patients from group 1 or 2 had cardiac events. However, 6 (14%) with severe endothelial dysfunction had 10 cardiac events (P	3 groups: group 1 (n=83), patients with normal endothelial function; group 2 (n=32), patients with mild endothelial dysfunction; and group 3

Mayo Foundation			<0.05 versus groups 1 and 2). Cardiac events included myocardial infarction, percutaneous or surgical coronary revascularization, and/or cardiac death.	(n=42), patients with severe endothelial dysfunction.
Suzuki 2002[133] Funding Unknown	Prospective cohort of 86 subjects with microvascular angina with normal coronary angiograms.	Mean follow-up time was 7.2±3.4 years (range, 2.8–11.6 years).	One patient (1.2%) died from leukemia, and 6 patients (7.1%) were readmitted to hospital during the follow-up period. There were no deaths from cardiac events. Of the 6 admissions during the follow-up period, 3 were for angina pectoris and cardiac catheterization was again carried out in 2 of them; however, no significant stenosis of the coronary arteries was observed.	Questionnaires regarding their symptoms, cardiac medication, occurrence of new events and hospital admissions were sent to all patients.
Takatsu 2011[134] Funding n/a	Prospective cohort study of 1266 consecutive patients with VAP without significant organic stenosis.	1248 patients with follow up data. The mean follow-up period was 11.7±6.8 years	Of the 121 patients with MACE or SD, the mean event-free duration was 6.7±5.8 years after the diagnostic angiogram. A total of 95 patients (88 males and 7 females) died because of noncardiac disorders. 91 patients (7.3%) developed MACE, including 33 patients with unstable angina, 43 patients with nonfatal myocardial infarction, and 15 patients with exertional angina.	Follow-up via medical record and telephone calls.
Voelker 1991[135] Funding n/a	Prospective cohort of 121 of 1050 consecutive patients with chest pain, in whom coronary artery disease was suspected and coronary	88/121 had full follow up. Mean length of follow-up was 9.2 years (6-11 years).	Three of these patients died during follow-up (two noncardiac deaths and one death with no etiology). One patient suffered a documented myocardial infarction.	?single site, does not explicitly state where patients recruited from

	cath revealed normal coronary arteries without luminal irregularities.			

Table 2: Other abstracted study summaries

Author/year/ funding	Methods/ Participants	Intervention	Main outcomes	Notes
Papanicolaou 1986[79] **Funding: unknown**	Retrospective cohort study of 7317 undergoing cardiac catheterizations for suspected ischemic heart disease. 1491 had Normal (less than 25% narrowing) 486 had "insignificant" stenoses (less than 75% narrowing). 4292 with significant disease	follow-up for a median of 6.3 years	1,898 patients with complete follow up, All-cause mortality: 50 12 cardiac deaths were documented, including 2 probable myocardial infarctions, 7 sudden deaths and 3 unobserved deaths. Excellent **cardiac survival** prognosis of the patients with insignificantly narrowed or normal coronary arteries compared to those with significant CAD is shown by 99% survival at 5 years and over 98% survival at 10 years in both groups without significant disease. **29 nonfatal myocardial infarctions** were also documented during follow-up: 22 definite, 4 probable and 3 possible. The Kaplan-Meier estimates of infarction-free survival at 1,5 and 10 years were lOO%, 99% and 98% for normal patients vs. 99%, 97% and 90% for patients with insignificant disease.	
Pitts 1997[64]	Retrospective analysis of over 10K catheterizations at a single site over	Repeat Cath 17 patients underwent second cath at a mean of 8.9 + 3.3 years	2 patients (patients 2 and 3) developed single-vessel coronary artery disease, 1 of whom had a myocardial infarction. Thus, 15 of the	No comparison group.

	27 years identifying 17 subjects with a previously normal cath angiography		17 subjects had no angiographically demonstrable coronary artery disease.	
McMullan 2011[60]	Retrospective natural history chart review of 129 adult patients found to have normal coronary arteries during angiogram. Normal was defined, a priori, as absence of any angiographic abnormality, including minimal luminal irregularity and non-critical stenosis.	The natural course of those with angiographically normal coronary arteries was followed through medical record review for 5 years after the date of the initial angiogram.	Complete 5-year medical records were available for 70 of the 129 patients. Survival for the remaining 59 patients was determined by SSDI review. Observed all-cause mortality was 10.1% (13/129, 95CI 5.7% to 16.9%). Among those who died, median survival was 106 weeks (0 to 246 weeks). **All-cause mortality: 13 With 3 cardiac** , multi-organ system failure in 2, ischemic stroke in 1, malignancy in 1, and unknown in 6 (determined by SSDI review). 15 patients who underwent repeat Angiography and new angiographic lesions were found in 6 (40.0%; 95CI 19.8% to 64.3%). Patients developed coronary heart disease between 2 and 5 years after initial angiogram.	Six of the subjects who did not survive were identified as dead from review of the Social Security Death Master File; therefore, specific causes of death cannot be determined. Also, only 15/129 underwent repeat angiography. Even if the 13 deaths are added that means 78% (101/129) did not have a repeat evaluation for development of CHD.
Wang 2015[63]	Retrospective review of hospital cath database. 366/2983 patients with ≤50% stenosis 158 had no stenosis 208 had 0-≤50% stenosis	enrolled over 15 months, then followed for 1 year	At 1 year, readmission with chest pain was 6.0%. The 1-year composite mortality and MACE rate was 1.9%, including one MI (0.3%) and one stroke (0.3%). No differences in outcomes were observed between those with angiographically normal arteries and mild CAD. During the complete "long term follow up" period (out through January 2013; between 22 – 36 months	Single center; many patients in this series were referred directly for coronary angiography, without non-invasive investigation on the basis of their symptoms and in many cases, patients been rendered symptom free with only modest pharmacotherapy.

			depending upon when the subject was enrolled in the study period) showed MACE rates of 4.1% (15).	
Tavella 2016[62]	Retrospective review of patients with chest pain undergoing elective angiography at 2 hospitals in Adelaide. 758 patients, 253 (33%) had insignificant CAD (<50% stenosis in any vessel)	758 patients, 253 (33%) had insignificant CAD (<50% stenosis in any vessel)	In one year follow up, there was one non-fatal MI and no deaths in those with insignificant CAD. In addition, there was a 4% ED repeat chest pain presentation, and 3% were readmitted. In addition, almost 50%	similar number of ICAD and CAD patients were pain-free at 1 month following angiography (30 vs. 29%, respectively, P . 0.05). by 6 months, there were fewer ICAD patients free of chest pain (39 vs. 55%, respectively, P , 0.05), although, by 12 months, the proportion of patients free of symptoms was similar in ICAD and CAD patients (48 vs. 59%,)

2. **Summary effect tables** (will give info for summary Evidence tables)

Table 3: RADICO[59] – subjects with 0% stenosis on catheterization (24 studies)

Outcome (~5yrs)	No. of subjects: 0% stenosis	Results for 0% (n)	Absolute risk per 1000 (95% CI)
combined incidence of all-cause death and myocardial infarction	12018	695	**695/12018 = 0.0578**
Non-fatal myocardial infarction.		**347**	**347/12018 = 0.0288**
All-cause mortality.		348	**348/12018 = 0.0289**

Table 4: Radico[59] - subjects with 1-49% stenosis or unspecified on catheterization (20 studies)

Outcome	No Subjects: 1-49% or unspecified	Results for 1-49%	Absolute risk per 1000 (95% CI)
combined incidence of all-cause death and myocardial infarction	8719	**818**	**818/8719= 0.0938**

Non-fatal myocardial infarction.	374	**0.0428**	
All-cause mortality.	444	**0.0509**	

1489

1490 **Table 5:** Results from other included studies

Study	Outcome	No. of subjects intervention	Results	Absolute risk per 1000 (95% CI)
Papanicolaou 1986[61]	**Over 10yrs** combined incidence of all-cause death and myocardial infarction Non-fatal myocardial infarction. All-cause mortality.	1898 patients	12 cardiac deaths over 10 years out of 1898 patients with complete data (**does not make a clear distinction if these deaths were in none vs insignificant group**s). 29 MI events among those with none or insignificant lesion (similar caveats)	**Combined MACE:** 41/1898 = 2.16% over 10 years **MI:** 29/1898 = 1.5% **Death:** 12/1898 = 0.63%
Pitts 1997[64]	combined incidence of all-cause death and myocardial infarction Non-fatal myocardial infarction. All-cause mortality.		2 patients developed ACS (LAD occlusion) at 4.8 and 4.9 years after negative cath.	2/17 = 11.7% risk of ACS at 5 years. NO death
McMullan 2011[60]	combined incidence of all-cause death and myocardial infarction Non-fatal myocardial infarction. All-cause mortality.	129 patients	all-cause mortality: 13 **Presumed cardiac death 3 + 6 (unknown)** Among those who died, median survival was 106 weeks (0 to 246 weeks). 6/15 who underwent repeat cath had new abnormalities c/w CHD = 40.0%;	all-cause mortality was 10.1% (13/129, 95CI 5.7% to 16.9%). Cardiac death 9/129 = 6.9% 6/15 who underwent repeat cath had new abnormalities c/w CHD = 40.0%; 95CI 19.8% to 64.3%.

			95CI 19.8% to 64.3%. Patients developed coronary heart disease between 2 and 5 years after initial angiogram.	
Wang 2015[63]	Outcomes at 1 year and during long-term follow-up were documented, focusing on readmissions with chest pain and major adverse cardiovascular events (MACE; death, myocardial infarction or revascularisation) using the Academic Research Consortium (ARC) definition. See table	158 had no stenosis 208 had 0-≤50% stenosis	**At 1 year:** NO stenosis – MACE= 3/158 = 1.89% ≤50% stenosis – MACE= 4/208 – 1.92% Aggregate MACE 7/366 = 1.9% **Total follow-up over 36-month study period:** NO stenosis – MACE= 5/158 = 3.16% ≤50% stenosis – MACE= 9/208 – 4.3% Aggregate MACE 15/366 = 4.1%	
Tavella 2016[123]	Outcomes at 12 months (death and MI)	758 patients, 253 (33%) had	Nonfatal MI 1/253 (0.395%);	Unclear how these outcomes were assessed. No mention if these were from secure records or self-report.

		insignificant CAD (<50% stenosis in any vessel)	0/253 deaths in those with insignificant CAD. 4% (n=10?) for ED repeat chest pain visits and 3(n=8?) were readmitted for angina.	

3. **Risk of bias/Quality assessment** of the include studies

Table 6. Risk of Bias – The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomized Studies in Meta-Analysis

Cohort studies

	Selection				**Comparability**	**Outcome**		
Author/ Year	**Representativeness of the exposed cohort**	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts
Papanicolaou 1986	*	-- No control	*	*	-- No controls	*	*	*
Pitts 1997	-- Highly Selected because of repeat cath	-- No control	*	*	-- No controls	*	*	*
McMullan 2011	*	-- No control	*	*	-- No control	*	*	*
Wang 2015	*	-- No control	*	*	-- No control	*	*	*
Tavella 2016	*	No control	*	*	**No control**	--	*	*

		(control arm was used for differed outcomes)						

(Max of 9 stars)

Risk of Bias – Studies included in Radico

Cohort studies

	Selection				**Comparability**	**Outcome**		
Author/ Year	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts
Addison 2014	*	*	*	*	*	*	*	*
Bugiardini 2004	-- **Only included women**	-- No control	*	*	-- No control	*	*	*
Cortigiani 2014	-- **highly selected with only T2DM patients**	-- No control	*	*	-- No control	*	*	*
Isner 1981	*	-- No control	*	-- There were patients with prior MI included	-- No control	*	*	*
Jespersen 2011	*	*	*	*	**	*	*	*
Kaski 1995	*	-- No control	*	*	-- No control	*	*	*

Lamendola 2010	*	-- No control	*	*	-- No control	*	*	*
Leu 2005	*	-- No control	*	*	-- No control	*	*	*
Li 2012	*	-- No control	*	*	-- No control	*	-- 6 months	*
Lichtlen 1995	*	-- No control	*	*	-- No control	*	*	*
Lim 2016	*	-- No control	*	*	-- No control	*	*	*
Marks 2004	**-- (selected cohort)**	-- No control	*	*	-- No control	*	*	*
Masumoto 2001	--	-- No control	*	*	-- No control	*	*	*
Nitenberg 2004	--	*	*	*	*	*	*	*
Nitenberg 2005	*	-- No control	*	*	-- No control	*	*	*
Pasternak 1980	*	-- No control	*	*	-- No control	*	*	*
Proudfit 1980								
Sakata 2005	*	-- No control	*	*	-- No control	*	*	*
Sanchez-Recalde 2009	Pending request for full manuscript to assess							
Schindler 2003	*	--	*	*	-- No control	*	*	*

		No control						
Schofield 1988	*	-- No control	*	*	-- No control	--	--	--
Scholl 1988	*	-- No control	*	-- 3 ppl with prior MI	-- No control	*	*	*
Sedlak 2013	*	-- No control	*	*	-- No control	*	*	*
Shin 2012	*	-- No control	*	*	-- No control	*	*	*
Shin 2015	*	-- No control	*	*	-- No control	*	*	Significant losses to f/u
Shintani 2003	*	-- No control	*	*	-- No control	*	*	*
Sicari 2005	*	-- No control	*	*	-- No control	*	*	*
Sicari 2009	*	-- No control	*	*	-- No control	*	*	*
Sullivan 1994	*	-- No control	*	*	-- No control	*	*	*
Suwaidi 2000	*	-- No control	*	*	-- No control	*	*	*
Suzuki 2002	*	-- No control	*	*	-- No control	*	*	*
Takatsu 2011	*	-- No control	*	*	-- No control	*	*	*

Voelker 1991	*	-- No control	*	*	-- No control	*	*	*

5. Summary of Evidence

Comparison	Outcome (5 years):	Study design (# studies)	Findings	Level of Evidence*	Overall evidence type
#4: Negative cardiac cath (less than 50% stenosis) and risk of subsequent ACS/time to ACS.	combined all-cause death and myocardial infarction	23 studies including 21 from Radico meta-analysis. All cohort or case-control	869 events in 11078 patients = 7.84%	**2 (meta-analysis)?**	**2**
	Non-fatal myocardial infarction.		404/11078 = 3.6% MI		
	All-cause mortality.		465/11078 = 4.1%		
#5: Negative cardiac cath (NO stenosis) and risk of subsequent ACS/time to ACS.	combined all-cause death and myocardial infarction	27 studies including 25 from Radico meta-analysis. All cohort or case-control	721 deaths/MI in 12322 patients with normal coronary anatomy: 5.8% absolute risk over approximately 5 years	**2 (meta-analysis)?**	**2**
	Non-fatal myocardial infarction.		355/12322 pooled patients = 2.88% absolute risk		
	All-cause mortality.		366/12322 = 2.97% absolute risk		
MACE: cardiac death, myocardial infarction or revascularisation) *Sackett DL. Rules of evidence and clinical recommendations on the use of antithrombotic agents. Chest 1989;95:2S–4S					

6. Moving from Evidence to Recommendation

Overall evidence type across all *critical* outcomes	2

1510

Outcome #4 (≤50% stenosis)	Values and Preferences
MACE: combined all-cause death and myocardial infarction at 5 years	
Non-fatal myocardial infarction.	
All-cause mortality.	

1511

Outcome #5 (0% stenosis)	Values and Preferences
MACE: combined all-cause death and myocardial infarction at 5 years	
Non-fatal myocardial infarction.	
All-cause mortality.	

1512

1513

Appendix 5: Evidence Retrieval, Assessment, and Synthesis for Question 7

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?

Included Studies: A total of 5,252 titles were reviewed, 338 articles selected for full text review, 17 studies were included for PICO#8, and 1 met the inclusion criteria for indirect evidence and was selected to create this recommendation. An additional 83 articles were reviewed and 2 met indirect inclusion criteria

a. Kim Y, Soffler M, Paradise S, et al. Depression is associated with recurrent chest pain with or without coronary artery disease: A prospective cohort study in the emergency department. American heart journal 2017; 191:47-54.[79]

Summary: This was a prospective cohort study of low– to moderate–cardiac risk ED patients ≥ 30 yrs old who were ruled out for acute infarction and admitted to Yale Chest Pain Center (CPC), an observation unit. Admitted subjects had a Thrombolysis in Myocardial Infarction score between 0 and 2. All patients also underwent appropriate cardiac stress testing with the assessment of cardiac risk factors to assess underlying coronary disease. At the time of enrollment, depression, anxiety, and perceived stress were assessed using validated scales: Patient Health Questionnaire (PHQ8), Clinical Anxiety Scale (CAS), and Perceived Stress Scale (PSS) respectively, providing baseline psychological assessment on presentation among other appropriate demographic, clinical and laboratory data. Depression (PHQ8 ≥ 10), anxiety (CAS ≥ 30), and perceived stress (PSS ≥ 15) were considered positive. Of 500 enrolled patients, 483 patients had complete data and 365 (76%) patients completed follow-up. Thirty-six percent (n = 131) had

recurrent chest pain within 1 month. Patients with recurrent chest pain were younger and were more likely to be female, Hispanic in ethnicity, employed, and prescribed antidepressants or anxiolytics compared with patients without recurrent chest pain. Depression was more prevalent in the recurrent population (26% vs 13%). Clinical anxiety diagnosed by CAS was highly prevalent in both groups (412 patients total or 85% of all enrolled). Ninety-one (74%) patients with recurrent chest pain followed up with an outpatient physician versus 151 (65%) in the non-recurrent population. Ten patients, all with recurrent chest pain , revisited the ED or were admitted within the 30-day follow-up period. On multivariable regression models, depression (odds ratio [OR] = 2.11, 95% CI 1.18-3.79) was a significant independent predictor of 30-day chest pain recurrence after adjustment, whereas PSS (OR = 0.96, 95% CI 0.60- 1.53) and anxiety (OR = 1.59, 95% CI 0.80-3.20) were not. Similarly, there was a direct relationship between psychometric evaluation of depression (via PHQ8) and the frequency of chest pain. They found patients with recurrent chest pain to have high rates of health services utilization (outpatient visits, ED visits, and hospitalizations).

Conclusion: This study suggests that depression, anxiety, and stress are prevalent in the chest pain population, but further establish that depression alone is independently associated with RCP, which leads to recidivism. Approaches to screen and manage depression early in the ED chest pain center may have significant implications in curtailing recidivism and improve quality of life for these patients.

Limitations: Single center study and the data needs to be validated in larger cohorts. Selection bias - This was not consecutive patient enrollment and limited to patients admitted to the observation unit thus may have missed very low-risk and recurrent, low-

risk chest patients. Some patients lost at follow-up, possibly leading to under recognition of chest pain recurrence.

b. Musey PI, Jr., Patel R, Fry C, Jimenez G, Koene R, Kline JA. Anxiety Associated With Increased Risk for Emergency Department Recidivism in Patients With Low-Risk Chest Pain. The American journal of cardiology 2018.[81]

Summary: This was a single center prospective observational cohort study of patients presenting the ED with low-risk chest pain (HEART score 0-3). Subjects were evaluated on enrollment with the Hospital Anxiety and Depression Scale – Anxiety subscale (HADS-A). a total of 163 subjects were enrolled and stratified into two groups based upon HADS-A screening results. Group 1 (n=87 (53%)) – low anxiety (score <8) and Group 2 (n=76 (47%)) -high anxiety (score ≥ 8). At 45-day follow-up, chest pain recurrence was assessed by patient report, whereas ED utilization was assessed through chart review. The relative risk for high anxiety being associated with at least one 30-day ED return visit was 2.6 (95% CI 1.4 – to 4.7) which increased to 9.1 (95% CI 2.18 - 38.6) for 2 or more ED return visits. Occasional chest pain recurrence was reported by more subjects in the high anxiety group, 68% vs 47% (p=0.029).

Conclusions: In this cohort of low-risk chest pain subjects, the prevalence of abnormal anxiety symptoms was 47% and this was associated with a high rate of ED recidivism, chest pain recurrence, and a low rate of medical diagnoses.

Limitations: Anxiety symptoms assessed by screening tool and not by SCID or formal assessment. This was a convenience sample of subjects at a single hospital site and does not account for the patient population who would have presented either on nights or

weekends. ED visits were also included regardless of reason and may have been due to chest pain. Chest pain recurrence is subjective and prone to recall bias especially given the 6-week period of time assessed.

c. Schwarz J, Prashad A, Winchester DE. Prevalence and implications of severe anxiety in a prospective cohort of acute chest pain patients. Critical pathways in cardiology 2015;14:44-7.[82]

Summary: This was a prospective observational study of a registry of low to moderate risk chest pain patients meeting criteria for continued evaluation in the chest pain evaluation center (CPEC), an 8-bed observational unit. The outcomes for this investigation were to 1) establish the prevalence of anxiety in the CPEC registry and 2) make comparisons of presentation, evaluation, and outcomes for subjects with and without severe anxiety symptoms. Prevalence of anxiety was determined using GAD-7 scores for the entire CPEC Registry population. Comparisons were made between the subset of subjects with severe anxiety (GAD-7 score > 15) and the remainder of the subjects. Of the 151 patients 22 (14.6%) had severe anxiety (SA, n=22). There was no statistical difference regarding 30 day follow up with a PCP or other doctor for chest pain (p=0.439), or 30-day recidivism to the ED with chest pain (p=0.554).

Conclusion: In summary, anxiety is common in ED patients with chest pain with prevalence several fold higher than the general population. In the ED population, anxiety is markedly underdiagnosed. CAD risk factors and symptoms were similar between patients with and without severe anxiety suggesting that a diagnosis of anxiety does not identify patients suitable for an abbreviated or accelerated ACS evaluation.

Limitations: Sample size leaves the investigation underpowered to determine if SA group patients have significantly risk of repeat ED visits. Selection bias is a possibility, however patients concerned about documentation of psychiatric disease would be less likely to participate and would then serve to underestimate anxiety. Proving a causal relationship between the two conditions is not possible. As noted previously, interactions between anxiety, chest pain, and heart disease may confound the degree to which anxiety is a stand-alone diagnosis for subjects in this investigation

Table 1: Characteristics of included studies

Author/year	Methods/ Participants	Intervention	Main outcomes	Funding	Notes
Kim 2017[79]	Prospective Observational Cohort/ 483 low-moderate risk chest pain pts in obs unit	Depression (PHQ8≥10) more prevalent in the RCP population (26% vs 13). Anxiety- (CAS ≥30) highly prevalent- 412 (85%) of patients enrolled).	Prevalence of RCP was 36% for patients who completed follow-up. 27% if all enrolled patients successfully completed follow-up. Adjusted multivariable regression model - depression independently increased odds of 30-day RCP by 211% (OR = 2.11, 95% CI 1.18-3.79) Ten patients, all with RCP, revisited the ED or were admitted within the 30-day follow-up period	none	Stratified primarily by RCP v NRCP not by anxiety - depression screening status. Selection bias of subjects admitted to obs unit with low-mod risk. Excludes low, very low-risk. Stratified by recurrence of chest pain (outcome) instead of anxiety/depression screening although depression clearly linked to recurrence of both chest pain and ED recidivism. Likely recall bias on part of patient.

Musey 2018[81]	Prospective Observational Cohort/ 163 low-risk chest pain pts	Anxiety screening (HADS-A)	Prevalence of Abnormal anxiety was 47% (n=76). Relative risk for high anxiety being associated with at least one 30-day ED return visit was 2.6 (95% CI 1.4 – to 4.7) and this relative risk increased to 9.1 (95% CI 2.18 - 38.6) for 2 or more ED return visits.	Developing Diverse Researchers with InVestigative Expertise (DRIVE) Award to PIM from Indiana University	
Schwarz 2015[82]	Prospective observational registry cohort /151 chest pain subjects admitted to CPEC	Screening with GAD-7 for anxiety	no statistical difference regarding 30 day follow up with a PCP or other doctor about chest pain (p=0.439), or 30-day recidivism to the ED with chest pain (p=0.554).	Data collection was supported in part by the Clinical and Translational Science Institute (NIH grant 1UL1RR029890)	

3. Summary effect tables

Intervention: Screening for anxiety/depression

Study	**Outcome**	**No. of subjects intervention**	**No Subjects controls**	**Results for intervention**	**Results for control**	**Absolute risk per 1000 (95% CI)**	**Number Needed to Treat (if applicable)**
Kim 2017[79]	Healthcare use (PCP follow up)	RCP 131 Depression 34 (26.0) Anxiety 118 (90.1)	NRCP 234 Depression 31 (13.3) 93 (19) Anxiety 196 (83.8)	91 (74)	151 (64.5)	n/a	n/a
	Return ED visits	same	same	10 (7.6)	0 (0.0)		
						depression independently increased	

	Chest pain recurrence					odds of 30-day RCP by 211% (OR = 2.11, 95% CI 1.18-3.79)	
Study	**Outcome**	**No. of subjects intervention**	**No Subjects controls**	**Results for intervention**	**Results for control**	**Absolute risk per 1000 (95% CI)**	**Number Needed to Treat (if applicable)**
Musey 2018[81]	Return ED visits	76	87	56 ED visits (27 unique) ARI 35.5	16 ED visits (12 unique) ARC 13.7	AR: 44.1 (23.9 unique) RR 2.6 (95% CI 1.4 – to 4.7)	-4.6
	Chest pain recurrence	56	53	38	25	AR: 57.7 (38.6 if complete data) 47.1 67.8	-4.83
Study	**Outcome**	**No. of subjects intervention**	**No Subjects controls**	**Results for intervention**	**Results for control**	**Absolute risk per 1000 (95% CI)**	**Number Needed to Treat (if applicable)**
Schwarz 2015[82]	Healthcare use (PCP follow up)	22	129	4	32	23.8% 18.1 24.8	0.15
	Return ED visits	22	129	0	2	1.3% 0 1.6	0.63
	Chest pain recurrence	n/a					

4. Risk of bias/Quality assessment of the include studies

Table 3. Risk of Bias - The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomized Studies in Meta-Analysis

	Selection				**Comparability**	**Outcome**		
Author/ Year	**Representativeness of the exposed cohort**	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts
Kim 2017[79]	*	*	*		**	**-- (self-reported chest pain recurrence)**	*	
Musey 2018[81]	*	*	*		**		*	
Schwarz 2015[82]	*	*	*		**		*	

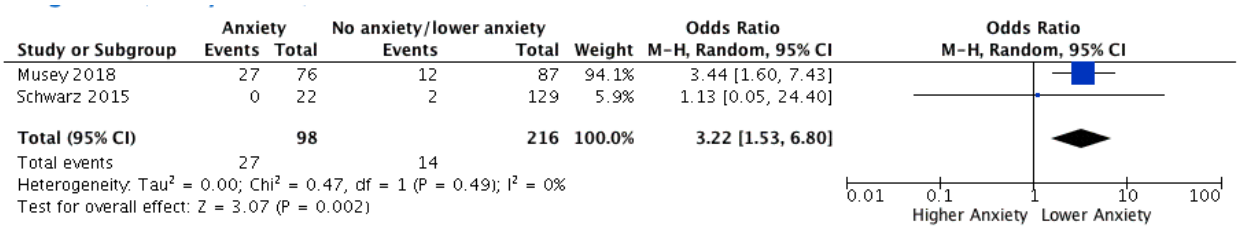
(Max of 9 stars)

5. Summary of Evidence

Comparison	**Outcome**	**Study design (# studies)**	**Findings**	**Level of Evidence**	**Overall evidence type**
Depression screening in low-risk chest pain	Chest pain recurrence 4-6 weeks	1	Kim shows Increased risk among Depression + Adjusted OR 2.11 (1.18-3.79)	4 (cohort/cas-control)	4
	ED Recidivism	1	Increased risk among Depression + group	4	

			Kim: 10/131 vs 0/234 ED return		
	Healthcare Use (hospital return)	1	Increased risk among Depression + group Kim: 5/131 vs 0/234	4	
Anxiety screening in low-risk chest pain	Chest pain recurrence 4-6 weeks	1	Musey shows increased risk among anxiety + Also, Kim showed no increased risk aOR 1.59 (0.80-3.79)	4	
	ED Recidivism	2	1 study shows increased risk among Anxiety + while 1 study shows no difference Kim: 10/131 vs 0/234 ED return Schwarz: 0/22 anxiety vs 2/129 return Musey: 27/76 vs 12/87	4	
	Healthcare Use	1	1 study shows difference 4/22 vs 32/129	4	

Figure: Pool of the Musey and Schwarz ED returns data



6. Moving from Evidence to Recommendation

Overall evidence type across all *critical* outcomes	4

Outcome	**Values and Preferences**
Chest pain recurrence 4-6 weeks	High value
ED Recidivism	Indeterminate
Healthcare Use	Relatively lower value

Appendix 6: Evidence Retrieval, Assessment, and Synthesis for Question 8

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

Included Studies: A total of 5,252 titles were reviewed, 338 articles selected for full text review, 18 studies were included for review PICO#8, and 2 meet the inclusion criteria and were selected to create this recommendation.

Kisely SR, Campbell LA, Yelland MJ, Paydar A. Psychological interventions for symptomatic management of non-specific chest pain in patients with normal coronary anatomy. *Cochrane Database Syst Rev*. 2015 Jun 30;(6):CD004101.[93]

Summary: This is a systematic review and meta-analysis which evaluated psychological interventions for symptomatic management of non-specific chest pain in patients with normal coronary anatomy. The authors included 17 RCTs with 1006 participants. Interventions included cognitive behavioral therapy, relaxation therapy, hyperventilation control, hypnotherapy, and other psychotherapy/counseling. There was a significant reduction in reports of chest pain in the first three months following the intervention (relative risk [RR] = 0.70 95% confidence interval [CI] 0.53 to 0.92). This was maintained from three to nine months afterward (RR = 0.59; 95% CI0.45 to 0.76). There was also a significant increase in the number of chest pain-free days up to three months following the intervention (mean difference [MD] = 3.00; 95% CI 0.23 to 5.77). This was associated with reduced chest pain frequency (MD = -2.26; 95% CI -4.41 to -0.12) but there was no evidence of effect on chest pain frequency from three to 12 months (MD = -0.81; 95% CI

-2.35 to 0.74). There was also no effect on severity up to three months after the intervention (MD = -4.64; 95% CI -12.18 to 2.89).

Conclusion: This study suggests a modest to moderate benefit for psychological interventions (particularly cognitive behavioral therapy), though it was primarily restricted to the first three months after the intervention.

Limitations: Findings are limited by absence of blinding, differences in outcome measures and assessment time periods, differences in study populations, differences in interventions, statistical heterogeneity, and wide confidence intervals.

Table 1. Studies included in Kisely et al[93].

Author/ Year	Methods/ Participants	Intervention	Main outcomes	Funding	Notes
Asbury 2007[136]	RCT; 53 female Syndrome X patients	Group 1: weekly autogenic training sessions with individual home program and symptom Group 2 (control): symptom diary only	The HADS Spielberger State-Trait Anxiety Inventory, Cardiac Anxiety Questionnaire, and the Ferrans & Powers Quality of Life Index were completed pre- and post-intervention and at 8-week follow-up	ND	ND
Asbury 2008[137]	RCT; 64 women with cardiac syndrome X	Group 1: 8-week phase III CR exercise program Group 2 (control): symptom monitoring	Hospital Anxiety and Depression Scales, Health Anxiety Questionnaire, and SF-36, energy, general health, Shuttle Walk Test, diastolic blood pressure and body mass index	ND	ND
Asbury 2011[138]	RCT; 49 women with cardiac syndrome X	Group 1: 12 monthly support group meetings Group 2 (control): usual care	The Health Anxiety Questionnaire (HAQ), HADS, SF-36, York Angina Beliefs scale, ENRICHD Social	ND	ND

			Support Instrument (ESSI) and a demographic information scale, along with hospital admissions, GP or cardiologist appointments were measured at baseline, 6 months, and 12 months		
DeGuire 1996[139]	RCT; 66 patients without an organic cause and symptoms occurring at least once per week	Group 1: Guided breathing retraining and physiological monitoring of diaphragmatic breathing and end-tidal CO_2 Group 2: Guided breathing retraining and physiological monitoring of diaphragmatic Breathing Group 3: Guided breathing retraining Group 4 (control): No treatment	Chest pain frequency and severity over 2 weeks, respiratory rate, mean end-tidal CO_2	ND	ND
Esler 2003[140]	RCT; 59 adult patients with low suspicion of CAD and negative chest pain evaluation in the ED	Group 1: One brief CBT intervention lasting 1 hour (included psychoeducation, cognitive restructuring and breathing exercises) Group 2 (control): usual care	Chest pain episodes over one month. Severity of episodes over one week and one month (chest pain visual analogue scale), SF-36, Cardiac Anxiety Questionnaire, Anxiety Sensitivity Index, and BSI at one month and three months.	ND	High attrition rate leading to potential follow-up bias.
Jones 2006[141]	RCT; 28 patients with angina-like chest pain with normal coronary angiogram and not	Group 1: 12 sessions of hypnotherapy or supportive therapy plus placebo medication over a 17 week period. Group 2 (control): No treatment	Global assessment of chest pain improvement; change in scores for quality of life, pain severity, pain frequency, anxiety, and depression; any	ND	81 eligible but only 28 entered the RCT

	esophageal reflux		alteration in the use of medication		
Jonsbu 2011[142]	RCT; 40 patients with persistent chest pain six months after a negative evaluation at a cardiology clinic	Group 1: Three CBT sessions, including one physical activity exposure session. Group 2 (control): Usual care	Health-related quality of life - the Body Sensations Questionnaire (BSQ), SF-36, frequency of symptoms of chest pain or palpitations, impact of cardiac symptoms on domains of family life, social life and work, and avoidance of physical activity at up to 3-month follow-up.	ND	Only half of eligible patients entered the study
Keefe 2011[143]	RCT; 63 adults with chest pain during the prior 6 months who had a negative stress test or angiogram within 2 years and low likelihood of CAD	Group 1: Coping skills training + sertraline Group 2: Coping skills training with placebo Group 3: Sertraline alone Group 4 (control): Placebo alone	Chest pain intensity and unpleasantness from pain diaries, State-Trait Anxiety Inventory, the 13-item Pain Catastrophizing Scale, the BDI, the physical disability scale of the Sickness Impact Profile (SIP), two items from Stone and Neale's Daily Coping Inventory, two items from the Coping Strategies Questionnaire were used to assess daily perceived pain control over pain	ND	ND
Klimes 1990[144]	RCT; 35 patients with chest pain at least once per week and normal cardiovascular exam	Group 1: 11 sessions over 3 months with CBT (including cognitive restructuring, problem solving, relaxation, breathing exercises) Group 2 (control): Behavioral explanation of symptoms	Chest pain free days and pain episodes over one week; 5-point activity avoidance scale; 8-point distress scale 8-point disruption of everyday life scale; PSE; STAI-T; BDI; SRT; Autonomic symptoms	ND	High drop-out rate

Lahmann 2008[145]	RCT; 22 patients with non-specific chest pain	Group 1: Psychosomatic education session followed by 10 group therapy sessions Group 2 (control): Usual care	Symptom Checklist of Derogatis (SCL-90), Giessen Inventory of Complaints (GBB)	ND	ND
Mayou 1997[146]	RCT; 37 patients with chest pain at least once per week without a cardiac diagnosis or major depression	Group 1: 12 CBT sessions (including cognitive restructuring, problem solving, relaxation, breathing exercises) Group 2 (control): Assessment only	Chest pain frequency, severity, distress over one month, and number of pain-free days over one week; 4-point scales of avoidance, limitation and impairment (leisure, work, family, overall); BSI; Whitely score	ND	High attrition rate
Potts 1999[147]	RCT; 60 subjects undergoing coronary angiography	Group 1: 6 CBT sessions (including education, cognitive restructuring, relaxation, breathing exercises, graded exposure, and light physical exercise) Group 2 (control): No intervention	Chest pain free days and pain episodes over one week; HV score; nitroglycerin dose per week; exercise duration (minutes); NHP; SIP; HADS	ND	Unclear attrition rate
Sanders 1997[148]	RCT; 57 patients undergoing coronary angiography	Group 1: Brief CBT intervention (including education, relaxation, breathing exercises, and graded exposure supplemented by a booklet and cassette tape of breathing and relaxation exercises) Group 2 (control): No intervention	Chest pain frequency, severity, distress, and number of pain-free days over one month; associated symptoms (i.e., palpitations and breathlessness); SF-36; SCL; STAI-T; BDI; Whitely score.	ND	High attrition rate
Spinhoven 2010[149]	RCT; 69 patients with non-cardiac chest pain as assessed in a	Group 1: CBT Group 2: Paroxetine Group 3 (control): No intervention	Frequency, duration, and intensity of chest pain; HADS; heart-focused anxiety by the Cardiac Anxiety	ND	High attrition rate

	cardiology clinic		Questionnaire (CAQ); M.I.N.I.-Plus		
Tyni-Lenne 2002[150]	RCT; 24 women with CCS Class II chest pain without HTN, DM, or systemic illness	Group 1: Physical endurance training three times per week for eight weeks Group 2: Relaxation training twice per week for eight weeks Group 3 (control): Normal daily activities	Peak oxygen uptake; peak work rate; distance walked during 6 minutes; rating of perceived exertion; SOC; SCI-93; SIP	ND	ND
Van Beek 2013[151]	RCT; 113 adult patients with non-cardiac chest pain who scored ≥ 8 on HADS	Group 1: 6 CBT sessions Group 2 (control): Reassurance by a cardiologist	Disease severity assessed with the CGI; HADS-anxiety; state trait anxiety inventory (STAI)-trait); Hamilton depression rating scale	ND	ND
Van Peski-Oosterbaan 1999[152]	RCT; 65 adult patients with non-cardiac chest pain as assessed by a cardiologist	Group 1: 12 CBT sessions (including cognitive restructuring, problem solving, relaxation, breathing exercises) Group 2 (control): Usual care	Chest pain free days and pain episodes including severity over one week; HADS; SF-36;Health service use	ND	High attrition rate

ND, Not described

Wang W, Sun YH, Wang YY, Wang YT, Wang W, Li YQ, Wu SX. Treatment of functional chest pain with antidepressants: a meta-analysis. Pain Physician. 2012 Mar-Apr;15(2):E131-42.[94]

Summary: This is a systematic review and meta-analysis which evaluated antidepressants for symptomatic management of functional chest pain. The authors included 7 RCTs comprising 319 patients. The median duration was 5 weeks (range: 3 to 16 weeks). There was strong evidence for an association of antidepressants with reduction in pain (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 (odds ratio = 0.34; 95% CI 0.15 to 0.78). There was no statistically significant improvement in health-related quality of life (weighed mean difference = 2.00; 95% CI - 2.54 to – 6.65).

Conclusion: This study suggests that antidepressant medications are associated with improvements in pain and psychological symptoms. There was no statistically significant difference in health-related quality of life.

Limitations: Small number of patients overall. There was limited reporting of demographics, comorbidities, or concomitant interventions, limiting the ability to assess for bias or confounding. Differences in intervention medications. There was statistical heterogeneity. There were also wide confidence intervals for health-related quality of life.

Table 2. Studies included in Wang et al.

Author/ Year	Methods/ Participants	Intervention	Main outcomes	Funding	Notes
Cannon 1994[153]	RCT; 60 patients without severe somatic disease, cardiovascular disease, or hypertension	Group 1: Imipramine Group 2 (control): Placebo	Pain diary, Pain visual analog scale	ND	ND
Cox 1998[154]	RCT Crossover; 36 women without cardiovascular disease or concomitant medications	Group 1: Imipramine Group 2 (control): Placebo	Pain diary, Nottingham Health Profile questionnaire	ND	ND
Doraiswamy 2006[155]	RCT, 69 patients without concomitant medications, panic disorder, major depression, substance abuse, or suicide risk	Group 1: Paroxetine Group 2 (control): Placebo	Pain visual analog scale, Clinical Global Impression	ND	ND
Spinhoven 2010*[149]	RCT, 69 patients without cardiovascular disease, concomitant medications, or mental disorders	Group 1: Paroxetine Group 2 (control): Placebo	Pain visual analog scale, HADS	ND	ND

Varia 2000[156]	RCT, 45 patients without panic disorder, major depression, substance abuse, severe somatic disease	Group 1: Sertraline Group 2 (control): Placebo	Pain visual analog scale, BDI, SF-36	ND	ND
Zheng 2006[157]	RCT, 121 patients without cardiovascular disease, severe somatic disease, pregnancy or breastfeeding, or schizophrenia	Group 1: Fluoxetine Group 2 (control): Placebo	Pain visual analog scale, HAMA, HAMD	ND	ND
Lee 2010[158]	RCT Crossover, 75 patients without severe somatic disease, mental disorders, or autonomic or peripheral neuropathy	Group 1: Venlafaxine Group 2 (control): Placebo	Pain visual analog scale, BDI, SF-36	ND	ND

**Study used in both SRMAs*

3. Summary Effect Tables

Table 3. Referral for Anxiety/Depression

Outcome	Number of subjects (intervention)	Number of Subjects (controls)	Results for intervention	Results for control	Absolute risk per 1000	Number Needed to Treat	Standardized mean difference (95% CI)
Any chest pain (<3 months)	90	82	57 (63.3%)	76 (92.7%)	29.4%	4	N/A
Any chest pain (3-12 months	50	61	27 (54%)	57 (93.4%)	39.4%	3	N/A
Chest pain frequency (< 3 months)	154	140	N/A	N/A	N/A	N/A	-2.26 (-4.41 to -0.12)
Chest pain frequency (3-12 months)	84	80	N/A	N/A	N/A	N/A	-0.81 (-2.35 to 0.74)

Reduction of chest pain (mean difference)	120	118	N/A	N/A	N/A	N/A	−1.26 (−2.43 to −0.13)

4. Risk of Bias

Table 4. Risk of Bias for Kisely et al

Author/ Year	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting
Asbury 2007[136]	U	L	H	H	L	L
Asbury 2008[137]	L	L	H	H	L	L
Asbury 2011[138]	L	L	H	H	H	L
DeGuire 1996[139]	U	U	H	U	H	L
Esler 2003[140]	U	L	H	H	H	L
Jones 2006[141]	L	U	H	L	L	L
Jonsbu 2011[142]	L	L	H	H	L	L
Keefe 2011[143]	L	L	H	H	L	L
Klimes 1990[144]	U	U	H	L	L	L
Lahmann 2008[145]	U	U	H	H	L	U
Mayou 1997[146]	L	L	H	U	H	L
Potts 1999[147]	U	U	H	U	U	L
Sanders 1997[148]	U	U	H	U	H	L
Spinhoven 2010[149]	L	L	H	H	H	U
Tyni-Lenne 2002[150]	U	U	H	U	U	L
Van Beek 2013[151]	L	L	H	L	H	L
Van Peski-Oosterbaan 1999[152]	U	U	H	U	H	L

L, low-risk; U, unclear risk; H, high risk

Table 5. Risk of Bias for Wang et al.

Author/Year	Jadad Score
Cannon 1994[153]	4
Cox 1998[154]	4
Doraiswamy 2006[155]	5
Spinhoven 2010*[149]	5
Varia 2000[156]	5
Zheng 2006[157]	5
Lee 2010[158]	5

5. Summary of Evidence

Comparison	Outcome	Study design (# studies)	Findings	Evidence type	Overall evidence type
Psychotherapy Interventions vs Control	Any chest pain (<3 months)	3	Decreased risk among intervention group	2	2
	Any chest pain (3-12 months	2	Decreased risk among intervention group	2	
	Chest pain frequency (< 3 months)	7	Decreased risk among intervention group	2	
	Chest pain frequency (3-12 months)	4	No difference	2	
Antidepressants vs Placebo	Reduction of chest pain (mean difference)	7	Decreased pain among intervention group	2	

6. Moving from Evidence to Recommendation

Overall evidence type across all *critical* outcomes	2

Outcome	Values and Preferences
Any chest pain (<3 months)	High value
Any chest pain (3-12 months	High value
Chest pain frequency (< 3 months)	High value
Chest pain frequency (3-12 months)	High value
Reduction of chest pain (mean difference)	Relatively lower value

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