

Draft Comparative Effectiveness Review

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Noninvasive Testing for Coronary Artery Disease

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Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
540 Gaither Road
Rockville, MD 20850
www.ahrq.gov

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Prepared by:

To Be Added for Final Version

Investigators:

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Preface

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

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

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

We welcome comments on this systematic review. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

Richard G. Kronick, Ph.D.
Director
Agency for Healthcare Research and Quality

David Meyers, M.D.
Acting Director, Center for Evidence and
Practice Improvement
Agency for Healthcare Research and Quality

Stephanie Chang, M.D., M.P.H.
Director, EPC Program
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

Elisabeth Kato, M.D., M.R.P.
Task Order Officer
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

Investigator Affiliations

To Be Added for Final Version

Acknowledgments

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Key Informants

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

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

The list of Key Informants who participated in developing this report will be added for the final version.

Technical Expert Panel

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

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

The list of Technical Experts who participated in developing this report will be added for the final version

Peer Reviewers

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

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

The list of Peer Reviewers who participated in reviewing this report will be added for the final version.

Noninvasive Testing for Coronary Artery Disease

Structured Abstract

Objectives: This report evaluates the current state of evidence regarding effectiveness and harms of noninvasive technologies for the diagnosis of coronary artery disease (CAD) or dysfunction that results in symptoms attributable to myocardial ischemia in stable, symptomatic patients who have no known history of CAD.

Data Sources: Systematic searches of the following databases: Ovid MEDLINE[®], Cochrane Central, and Cochrane Database of Systematic Reviews (no publication date restrictions). Bibliographies of relevant articles were also reviewed.

Review Methods: Using predefined criteria, randomized trials and observational studies comparing the effectiveness or safety of noninvasive cardiac testing (stress electrocardiography [ECG], stress echocardiography, single photon emission computed tomography [SPECT], positron emission tomography, coronary computed tomography angiography [CCTA], and calcium scoring via computed tomography) with other noninvasive tests, usual care, or no testing were included. Analyses were stratified by pretest risk of CAD as reported by the authors. The quality of included studies was assessed, data extracted, and results summarized qualitatively and using meta-analysis where feasible. The strength of the evidence was graded for primary outcomes.

Results: Of 17,146 citations identified, 45 studies were included. Definition of pretest risk across studies was variable. There was no clear difference in myocardial infarction or all-cause mortality between different testing strategies across settings or pretest risk groups that included intermediate pretest risk patients based on low (for CCTA vs. usual care and SPECT vs. ECG) and moderate (for CCTA vs. functional testing) strength of evidence. Invasive coronary angiography (ICA) was common following CCTA compared with various functional tests with a large trial of CCTA versus functional testing providing highest strength of evidence. Revascularization referral was more common following CCTA versus functional testing in general (high strength of evidence) and versus exercise ECG (low strength of evidence) but was similar compared with SPECT and usual care (low strength of evidence). In emergency department settings, additional testing following CCTA was more common compared with SPECT (high strength of evidence) but less common versus usual care (moderate evidence). Hospitalization was less common following CCTA versus usual care at initial emergency department visit (moderate evidence for intermediate pretest risk; low evidence for low to intermediate pretest risk) but similar versus functional testing in outpatient settings (moderate strength of evidence). Few studies compared functional tests; findings were inconsistent for ICA and revascularization referral; however, additional noninvasive testing was less common with SPECT versus exercise ECG (low strength of evidence for all outcomes). The impact of testing on posttest probability of CAD and subsequent clinical decisions regarding treatment or further testing was not described in randomized controlled trials. Harms were rarely reported and limited information regarding radiation exposure was provided.

Conclusions: There were no clear differences between testing strategies across settings with regard to clinical or management outcomes to recommend one strategy over another for any given pretest risk group that included intermediate pretest risk patients. No conclusions regarding

low risk patients or those without acute coronary syndrome at high risk are possible. Limited evidence from randomized controlled trials found no clear differences between CCTA versus other strategies in clinical outcomes across risk groups, though anatomic testing may result in a higher frequency of referral for ICA and revascularization. The absence of information on posttest risk stratification and subsequent decision making precluded evaluation of the impact of testing on patient management or outcomes of management. Testing strategies vary in radiation exposure; there is inadequate comparative evidence to make judgments regarding exposure for initial test or downstream testing. Assessment of harms was limited. Future research using more refined, evidence-based definitions of pretest risk coupled with information on posttest risk stratification, its impact on clinical management (treatment and referral for additional testing) and longer term follow up to assess clinical outcomes are needed to determine optimal testing strategies and roles of tests in different pretest risk groups.

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Executive Summary

Background

Nature and Burden of Coronary Artery Disease

The public health and economic burdens of coronary artery disease (CAD) are substantial. CAD causes one in six deaths in the United States and is the leading cause of death globally.¹ Annually, approximately 635,000 Americans experience a new coronary event, 280,000 will have a recurrent ischemic event, and an additional 150,000 will have a silent first myocardial infarction (MI).² A large proportion of ambulatory health care visits are for evaluation of patients with suspected CAD, with an estimated 1.5 percent of the population presenting to healthcare providers with chest pain every year.³ An estimated \$108.9 billion is spent annually on CAD treatment.⁴ Optimizing the process for assessing these patients presents an opportunity to improve patient outcomes and target health resources to where they can have the most impact.

The most common underlying cause of CAD is atherosclerosis, a disease process in which plaque builds up on artery walls and can result in the partial or complete blockage of coronary arteries. As a result the heart cannot receive adequate blood, oxygen, and vital nutrients. Plaque causes blockage by two mechanisms: 1) progressive narrowing of the artery due to the plaque compromising the vessel lumen, and 2) thrombotic occlusion of the artery, which occurs when the hard surface of a plaque tears or breaks off and exposes the inner fatty pro-thrombotic and platelet-attracting components to the site, resulting in enlargement of the blockage. The resulting reduction in blood flow can be either acute or chronic and leads to an imbalance in the blood supply to the myocardium and thus increases the requirements of the myocardium for oxygenated blood either at rest or during exertion.^{5, 6}

The most common symptom of obstructive CAD is chest pain, which is the first presenting symptom in up to at least 50 percent of patients with CAD.⁷ Other common symptoms include the angina equivalents dyspnea, early fatigue with exertion, indigestion, palpitations, tightness in the throat, and neck or arm pain. However, because these symptoms are also seen in many common noncardiac conditions such as gastroesophageal reflux, esophageal spasm, and cervical disc disease, they are much less reliable predictors of CAD. Women and people with diabetes are less likely to experience classic angina, making early diagnosis of CAD challenging in these populations. The onset of symptoms and clinical impact of CAD depend on a variety of factors and don't necessarily correlate with symptoms. Further, CAD may remain asymptomatic for many years.

Diagnosis of CAD

Accurate, early diagnosis of CAD in symptomatic patients is important for initiation of appropriate treatment and reduction of CAD-related morbidity and mortality. Diagnosis of CAD begins with a thorough clinical work-up to include a physical examination, patient history, as well as obtaining some combination of a resting ECG, chest X-ray, and/or serum biomarkers such as cardiac troponins. If the presentation is not acute, the ECG is nonspecific, and cardiac troponins are normal, then the stable patient may be discharged or receive further testing to help determine the etiology of chest pain and the appropriate management.

A diagnosis of CAD can be made by looking for evidence of the pathophysiologic processes of disease, including anatomic changes of the arterial wall, impaired myocardial perfusion, or

consequences of impaired perfusion such as myocardial contractile dysfunction. Historically, invasive coronary angiography (ICA) has been considered the standard reference diagnostic test for anatomic CAD (defined here as any obstructive lesion that is consistent with symptoms or which may carry an increased risk of acute coronary syndrome [ACS]), although its invasive nature makes it less ideal in many patients due to its associated risks and costs. Noninvasive tests are another option, and provide diagnostic and prognostic information that can improve risk stratification and thus guide subsequent testing and interventions. Noninvasive diagnostic tests can be broadly divided into two categories: functional tests and anatomic tests. Functional tests provide additional information not provided by standard ICA, such as whether symptoms are correlated with areas of ischemia. Functional tests include exercise electrocardiography (ECG), exercise/pharmacologic stress echocardiography, exercise/pharmacologic cardiac nuclear imaging with single photon emission computed tomography (SPECT) or positron emission tomography (PET), pharmacologic stress magnetic resonance imaging (MRI), computed tomography (CT), and Doppler ultrasound-derived flow reserve measurements. Noninvasive anatomic tests include coronary CT angiography (CCTA) and coronary artery calcium scoring (CACS). American College of Cardiology Foundation/American Heart Association (ACCF/AHA) appropriate use criteria suggest that, as a general rule, functional testing is more informative than noninvasive anatomic evaluation and exercise testing is more informative than pharmacologic testing.⁸

Deciding which test use for diagnosis of CAD in stable symptomatic patients is not a simple matter. A patient's pretest CAD risk can inform which test or procedure is most appropriate as a first step towards diagnosing CAD. While there are a number of standard risk assessment tools, in clinical practice these are rarely documented and the clinician's overall assessment of sociodemographic characteristics (e.g., sex, age) and characteristics of the chest pain (typical or atypical) is the most common assessment of pretest likelihood of CAD. Pretest risk of CAD is frequently based on the ACCF/AHA Guidelines and defined as low (less than 10% pretest probability of CAD), intermediate (10%–90% pretest probability of CAD), or high (greater than 90% pretest probability of CAD). Patients at low pretest risk may undergo noninvasive testing to further delineate their risk and to provide a basis for clinical decision making, though in some cases, an alternate explanation for the symptoms (such as heartburn, costochondritis, or pulmonary disease) may be evaluated first. Patients at intermediate risk commonly undergo noninvasive testing followed by appropriate treatment for comorbidities and risk factors. The ACCF/AHA intermediate range is intentionally broad reflecting the availability of noninvasive tests that have been viewed as both safe and effective to further stratify risk in the "intermediate pretest risk" category. In other words, the low end of the intermediate range is extended irrespective of cost because of the important health consequences of missing disease, but also results in a situation where testing is performed in a very large number of individuals who do not have disease.⁹ The high end is extended because of the combination of the somewhat high cost and risk of ICA and reasonably high sensitivity of testing to detect high risk obstructive disease. Patients at high risk may undergo noninvasive testing, although at times clinicians may appropriately decide to bypass noninvasive stress testing and proceed directly to ICA.⁸ This is more frequently done in patients who present to the emergency room with typical symptoms. In patients where clinical judgment remains equivocal, an additional test to further identify risk may be pursued.

The 2012 ACCF/AHA guideline states that diagnostic testing is most valuable when the pretest probability of ischemic heart diseases is intermediate (10%–90%) and provides a range of

options for which test may be used in a given scenario. However, the effectiveness of different modalities with regard to impact on clinical outcomes are not compared.¹⁰ There remains uncertainty regarding which tests, if any, may be most suitable and most beneficial for specific patient scenarios in patients who present with symptoms suggestive of CAD. Specifically:

- In patients with low pretest probability of CAD (<10%), are clinical outcomes improved by use of stress testing with or without imaging or with no further testing? It is not clear whether imaging may be necessary in this group of patients or if there are specific subgroups of low risk patients who might benefit more from one type of testing or who should have no further testing.
- How do tests compare with regard to improvement in clinical outcomes (e.g., MI, premature mortality, and congestive heart failure) in very low (<5%) or low and in intermediate to high risk patients? How do tests differ in their ability to reclassify patient risk after the test and influence appropriate patient management?
- Are there differences in clinical outcomes following anatomic versus functional testing in either of the above risk groups?

Scope and Key Questions

The objective of this review is to assess the effectiveness of noninvasive technologies for the diagnosis of CAD or dysfunction that results in symptoms attributable to myocardial ischemia in patients who present with signs or symptoms suggestive of CAD, whose condition is considered to be stable, and who have no known history of CAD. The intended focus is on clinical outcomes and clinical pathways following the first diagnostic test performed as result of initial risk assessment (which includes clinical presentation and physical exam, family history of CAD, and findings on resting ECG). Further, this report focuses on established tests for diagnosing CAD. Harms related to both the initial test as well as subsequent testing will be evaluated. Information on traditional measures of accuracy (e.g., sensitivity and specificity) of noninvasive tests versus the historically accepted gold standard of ICA comprises the majority of the literature and is presented for context in the background. Increasingly, experts in cardiovascular health indicate that evidence on the value of noninvasive diagnostic cardiovascular testing needs to expand beyond traditional measures of test performance, such as sensitivity and specificity compared with a given reference standard and focus on evaluating the impact of such testing on hard cardiovascular outcomes and downstream harms. Thus, while diagnostic accuracy measures provide important information on test performance, the primary focus of this report is to determine whether noninvasive tests improve clinical health outcomes and impact patient management.

The Key Questions used to guide this report are provided below. The analytic framework (Figure A) shows the target population, interventions, and outcomes that were examined.

Key Questions

In stable, symptomatic patients with suspected CAD who do not have previously diagnosed CAD and who have had a resting ECG:

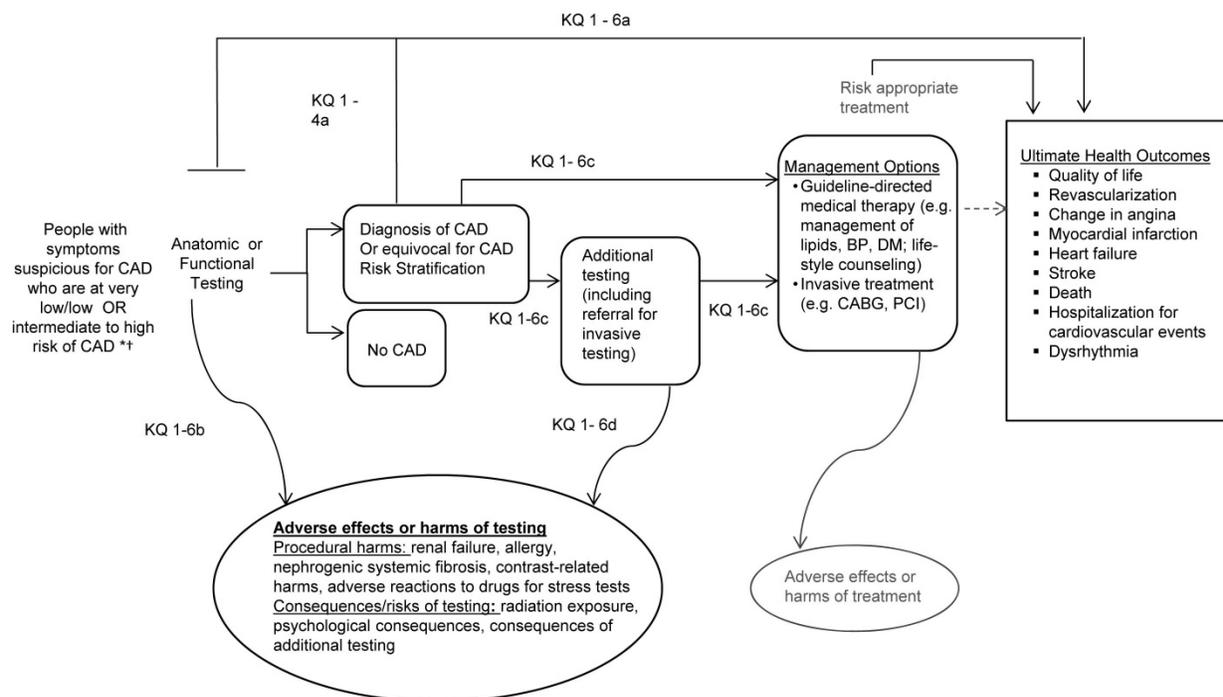
1. For patients considered to be at *very low or low risk* for CAD, what is the comparative effectiveness of **anatomic tests (compared with each other, usual care, or no testing)?**

2. For patients considered to be at *very low or low risk* for CAD, what is the comparative effectiveness of **functional tests (compared with each other, usual care, or no testing)**?
3. For patients considered to be at *intermediate to high risk* for CAD, what is the comparative effectiveness of **anatomic tests (compared with each other usual care or no testing)**?
4. For patients considered to be at *intermediate to high risk* for CAD, what is the comparative effectiveness of **functional tests (compared with each other, usual care, or no testing)**?
5. What is the comparative effectiveness of **anatomic tests versus functional tests** in those who are at *very low or low risk* for CAD?
6. What is the comparative effectiveness of **anatomic tests versus functional tests** in those who are at *intermediate to high risk* for CAD?

For each Key Question listed above, the following subquestions were explored:

- a. For improving primary clinical health outcomes (e.g., quality of life, avoiding myocardial infarction)?
- b. What are the adverse effects, consequences or harms of testing?
- c. How do noninvasive tests differ in terms of clinical management based on test results, including referral for coronary angiography or additional noninvasive testing?
- d. What harms are associated with additional testing following anatomic tests?
- e. Is there differential effectiveness or harm based on patient characteristics (e.g., sex, age, comorbidities) or the patient's ability to exercise?

Figure A. Analytic framework for noninvasive testing for coronary artery disease



*People at very low or low risk will be evaluated separately from those at intermediate to high risk as possible.

†KQ 1–6e: Potential modifiers related to differential efficacy and/or safety include patient factors (e.g., age, sex), comorbidities, and ability to exercise.

BP = blood pressure; CABG = coronary artery bypass graft; CAD = coronary artery disease; DM = diabetes mellitus; KQ = Key Question; PCI = percutaneous coronary intervention.

Methods

The methods for this Comparative Effectiveness Review (CER) follow the guidance in the Agency for Healthcare Research and Quality (AHRQ) Methods Guide for Effectiveness and Comparative Effectiveness Reviews.¹¹

Topic Refinement and Review Protocol

The topic for this comparative effectiveness review was ranked as a priority topic by a panel of stakeholders convened through the Duke Evidence-based Practice Center’s Cardiovascular Topic Identification project. The preliminary Key Questions were posted on AHRQ’s Web site for public comment for 4 weeks. Public comments and input from the Technical Expert Panel (TEP) were used to develop the final KQs and protocol. The TEP, convened to provide high-level content and methodological guidance to the review process, consisted of experts in cardiology and cardiac diagnostic testing, radiology, internal medicine, and health services research, as well as professional organizations and policy makers. TEP members disclosed all financial or other conflicts of interest prior to participation. The AHRQ Task Order Officer and the investigators reviewed the disclosures and determined that the TEP members had no conflicts of interest that precluded participation.

Both the final topic refinement document and the systematic review protocol, developed prior to initiation of the review, can be found on the AHRQ Web site at <http://effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/>. The protocol is also registered with the PROSPERO international database of prospectively registered systematic reviews (CRD42015022081).

Literature Search Strategy

A research librarian conducted searches for primary studies in the following databases through November 2014: Ovid MEDLINE[®], Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews. A search strategy was developed based on an analysis of the medical subject headings (MeSH), terms, and text words of key articles identified *a priori* (the full search strategy is available in Appendix A). Search start dates were not restricted. The reference lists of included articles and relevant review articles were also reviewed. All citations were downloaded and imported into an electronic database (EndNote[®] X7 Thomson Reuters, Philadelphia, PA). A list of relevant drugs and manufacturers was provided to the Scientific Resource for request of Scientific Information Packets and relevant published and unpublished studies were assessed for inclusion in the final report.

Due to the large number of citations retrieved by our database searches, two experienced team members created a list of search terms using the exclusion criteria in the PICOTS (populations, interventions, comparators, outcomes, timing, and setting) table and applied a systematic search in EndNote[®] in order to further exclude studies with a high likelihood of not being relevant. The full list of terms and methods used is available in Appendix A. Briefly, citations without abstracts, those not available in English, and certain publication types (case report, narrative review) were excluded. For the remaining citations, titles were searched for terms related to unequivocally excluded populations (e.g., stent, cardiomyopathy), interventions (e.g., ultrasound, Doppler, screening), and outcomes. The title was chosen as the search field because it should contain only terms most relevant to the purpose of the study. Out of a total of 17,146 citations, 8186 were excluded using this method.

Literature searches will be updated during the public comment and peer review period in order to ensure any new publications that meet our inclusion criteria are incorporated into the final report.

Inclusion and Exclusion Criteria

Criteria for inclusion and exclusion of studies were based on the Key Questions and the PICOTS approach. Briefly, studies of stable, symptomatic adult patients undergoing their first noninvasive diagnostic test for suspected CAD were sought. Patients with known CAD (prior MI or prior revascularization) were excluded. For all Key Questions, the focus was on evidence from comparative studies with the least potential for bias. Noncomparative studies of predictive accuracy were considered if there was a lack of comparative data for a specific diagnostic modality. Interventions of interest included anatomic imaging (i.e., CCTA, coronary calcium scoring via electron beam or multidetector CT) and functional tests (i.e., stress ECG, stress echocardiography, stress nuclear imaging [SPECT, PET], and stress MRI). Comparators included other noninvasive tests included in the interventions, usual care (as defined by the authors), or no testing. Studies that included technologies that are not widely available or no longer used, or have not been established for the diagnosis of CAD were excluded.

The primary outcomes (see Rating the Body of Evidence below) were considered to be the most clinically important and were the focus of reporting, decisions for data pooling, and determination of overall strength of evidence. Additional outcomes are reported in the detailed evidence synthesis sections of the Key Questions with a focus on outcomes common across studies. Where applicable and where data were available, results from the index visit and the followup period were reported separately. For studies of predictive accuracy, only hard clinical outcomes (i.e., MI, death, composite cardiac outcome, heart failure) were evaluated. For both the initial test and any subsequent downstream testing, the primary safety outcomes were related to harms of testing (e.g., adverse reaction or allergy to contrast or stress agents) and risks and consequences of testing (e.g., radiation exposure). Studies focused on “per-vessel” or “per-segment” analysis without per patient findings were excluded and treatments and outcomes of treatments were beyond the scope of this report.

Studies published only as conference abstracts, non-English-language articles, and studies of nonhuman subjects were excluded. Studies had to report original data to be included.

Study Selection

Abstracts for all citations from the literature searches were independently reviewed by two team members and results were recorded in EndNote. All citations found to be potentially appropriate for inclusion by either reviewer underwent full-text review. Each full-text article was independently evaluated for final inclusion by two investigators. For inclusion, both reviewers had to agree that inclusion criteria were met. Differences between reviewers were resolved through consensus and discussion. A record of studies excluded at the full-text level with reasons for exclusion is included in Appendix C.

Data Extraction

The investigative team created a form in Microsoft Excel for abstracting the data elements for the Key Questions. The data abstraction forms were piloted by two members of the team and refinements made as needed. Two staff members were responsible for abstracting demographic information for each study and five experienced team members entered data for the outcomes of interest. After data extraction, at least one other staff member and one investigator each verified the accuracy and completeness of abstraction for each study included. Discrepancies were resolved by discussion and consensus. An outline of the specific information included in the data extraction forms is available in Appendix D.

Quality (Risk of Bias) Assessment of Individual Studies

Predefined criteria were used to assess the quality (risk of bias) of included RCTs and observational studies by using clearly defined templates and criteria as appropriate and following guidance from the Agency for Healthcare Research and Quality (AHRQ) *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*.¹¹ Assessment of RCTs followed appropriate criteria and methods established in the Cochrane Handbook for Systematic Reviews of Interventions.¹² Comparative observational studies were assessed for study design features and sources of potential bias. These criteria and methods were used in concordance with the approach recommended in the chapter, Assessing the Risk of Bias of Individual Studies When Comparing Medical Interventions, in the AHRQ Methods Guide *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*, wherein each study was rated as being

“good”, “fair”, or “poor” quality.¹³ Two investigators independently assessed the quality of each study, and any discrepancies were resolved through discussion and consensus.

Briefly, studies rated “good” are considered to have the least risk of bias, and their results are considered valid. Studies rated “fair” are susceptible to some bias, though not enough to invalidate the results. The fair-quality category is broad, and studies with this rating will vary in their strengths and weaknesses. Studies rated “poor” have significant flaws that imply biases of various types that may invalidate the results. Studies rated as being poor in quality *a priori* were not excluded, but considered to be less reliable than higher quality studies when synthesizing the evidence, particularly if discrepancies between studies were present. The final quality assessments ratings are described in detail in Appendix I.

Data Synthesis

When adequate data were reported in at least two studies, meta-analysis was conducted in order to provide more precise estimates for outcomes. To determine the appropriateness of conducting meta-analysis, clinical and methodological diversity and assessed statistical heterogeneity were considered. Given the multiple interventions included in this report, a network meta-analysis was planned to estimate the relative effects of interventions that have not been directly compared, and to make full use of both direct and indirect evidence (Lu & Ades, 2006). However, the number of included studies turned out to be very small (two for each comparison) with limited number of comparisons (only CCTA vs. SPECT, and CCTA vs. usual care). Along with heterogeneity across studies, this made network meta-analysis impossible. Therefore, only standard meta-analysis was conducted and only binary outcomes were eligible. The profile-likelihood random-effects model¹⁴ was used to combine risk differences while incorporating variation among studies. The presence of statistical heterogeneity among the studies was assessed by using the standard Cochran’s chi-square test and the magnitude of heterogeneity by using the I^2 statistic.¹⁵

To account for clinical heterogeneity, we stratified analyses by pretest risk. Within each stratum, the number of studies was too small for exploring heterogeneity based on any study level characteristics. Sensitivity analyses using risk ratios were conducted to check the robustness of results to the choice of effect measure. Conclusions were generally similar and not separately reported. All analyses were performed using Stata/IC 12.1 (StataCorp, College Station, TX).

Rating the Body of Evidence

The following outcomes below were considered to be the most relevant and were the focus of reporting, data pooling, and determination of overall strength of evidence: mortality (all cause), MI, additional noninvasive testing, referral for ICA, and subsequent revascularization (i.e., percutaneous coronary intervention [PCI] or coronary artery bypass graft [CABG]). Primary safety outcomes of interest included (for both the index test and any subsequent downstream testing): harms of testing (e.g., renal failure, allergic reactions, and adverse reactions to contrast or stress agents) and risk and consequences of testing (e.g., radiation exposure, psychological consequences of diagnosis, incidental findings).

The strength of evidence (high, moderate, low, or insufficient) for each primary effectiveness and safety outcome described above was initially assessed by one researcher using the approach described in the AHRQ *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*, also available from the AHRQ Web site.^{11, 13} To ensure consistency and validity of the

evaluation, the strength of evidence ratings for all key outcomes were reviewed by the multiple investigators, and discrepancies were resolved by consensus.

Briefly, bodies of evidence consisting of RCTs started as high strength (greatest confidence that the evidence reflects the true effect and further research is unlikely to change our confidence in the effect estimate) while bodies of comparative observational studies began as low strength evidence (low confidence in the estimate; further research is likely to change the effect estimate and change the confidence in the estimate). The strength of the evidence was then downgraded based on study limitations (i.e., risk of bias, consistency of effect, directness of outcome, precision of effect estimate, and reporting bias; see AHRQ's *Methods Guide* for details¹¹). There are also situations where the observational evidence may be upgraded (e.g. very large size of effect), but we found no instances where these could be applied in this body of evidence (see AHRQ's *Methods Guide* for details on upgrading¹¹; see also AHRQ's *Methods Guide for Medical Test Reviews*¹⁶). The detailed strength of evidence tables and detailed explanations of the various grades can be found in Appendix J of the full report.

Applicability

Applicability of the evidence was considered by examining the characteristics of the patient populations included in studies (e.g., demographic characteristics, presence of relevant cardiac risk factors, pretest risk for CAD); the sample size of the studies; and clinical settings (e.g., outpatient clinic, emergency department [ED]) in which the studies are performed, as outlined in the AHRQ *Methods Guide*.^{11, 17} which is also available from AHRQ EHC website at <http://www.effectivehealthcare.ahrq.gov/ehc/products/272/603/Methods%20Guide--Atkins--01-03-2011KM.pdf>. Variability in the studies may limit the ability to generalize the results to other populations and settings, for example older studies of established tests may not be as applicable in light of advances in technology and short-term outcomes based on immediate decisionmaking in the ED may not be generalizable to longer-term outcomes and decisionmaking in the outpatient setting.

Peer Review and Public Commentary

Experts in the diagnosis and treatment of coronary artery disease as well as individuals representing other important stakeholder groups have been invited to provide external peer review of this Comparative Effectiveness Review. Comments and editorial review will also be provided by the AHRQ Task Order Officer. The draft report will be published on the AHRQ Web site for 4 weeks in order to solicit public comments. At the end of this period, the authors will consider both the peer and public review comments and generate a final report. A disposition of comments report detailing the authors' responses to the peer and public review comments will be made available 3 months after AHRQ posts the final report on the public web site.

Results

Results of Literature Searches

Database searches identified 17,146 potentially relevant citations. After dual review of abstracts and titles, 296 articles underwent review at full-text, and of these 45 studies (in 48

publications) were determined by dual review to meet the inclusion criteria and were included in this report. The evidence base in this report includes data from randomized controlled trials (RCTs) as well as observational studies and noncomparative studies. Studies designed to compare one noninvasive test to another (or to usual care or to no testing) form the primary basis for our report.

Organization of Results

Given the heterogeneity in how pretest risk was measured and defined across the studies, results could not be reported as delineated by the Key Questions into distinct pretest risk groups (i.e., low risk and intermediate to high risk). Therefore, the results were organized by pretest risk as defined by the study authors, which included low-risk, intermediate-risk, low- to intermediate-risk, intermediate- to high-risk, high-risk, and mixed-risk populations (or pretest risk not reported). Studies describing “high” pretest risk excluded patients with ACS and were interpreted as representing the higher risk end of the intermediate pretest risk range. Available data from studies conducted in EDs were primarily for the index ED visit and is noted. Outcomes such as MI at the time of the ED index visit were considered to reflect diagnosis of MI at that time. Where available, data on longer term followup is presented.

Given the focus of the report on evaluation of testing based on pretest risk, results for the low and high pretest risk groups are presented below even though evidence from these groups was rated as insufficient. Evidence for all other comparators and primary outcomes not listed below was insufficient to draw conclusions due to study limitations and/or imprecision in observational studies or due to lack of evidence.

Low Pretest Risk of CAD

A total of two RCTs were identified in populations with a low pretest risk of CAD: CCTA versus usual care (1 RCT)¹⁸ and SPECT versus exercise ECG (1 RCT).¹⁹ Evidence was based on subgroup analyses and was insufficient for all outcomes.

CCTA Versus Usual Care

- In a subgroup of 99 low-risk patients presenting to the ED, there is insufficient evidence from one fair-quality trial to draw conclusions regarding differences between CCTA and usual care in all-cause mortality (0% in both groups) or hospitalization for acute coronary syndrome (4% vs. 2%) through 30 days. At the time of ED (index) visit, frequency of ICA referral (6% vs. 10%, RD -4, 95% CI -15 to 7 per 100 people) and revascularization (6% vs. 2%, RD 4, 95% CI -4 to 12 per 100 people) was similar between CCTA and usual care, respectively (insufficient evidence).

SPECT Versus Exercise ECG

- In a subgroup of 71 low-risk outpatients, there is insufficient evidence from one fair-quality trial that SPECT patients had less additional noninvasive stress testing than exercise ECG patients (0% vs. 14%, RD -14, 95% CI -24 to -4 per 100 people) through a mean of 22 months. SPECT patients were slightly more likely to have ICA referral (7% vs. 0%, RD 7 per 100 people, $p=0.0690$) through the same followup period although the difference was not statistically meaningful (insufficient evidence).

Intermediate Pretest Risk of CAD

A total of six comparative studies (in 7 publications) were identified in populations with an intermediate pretest risk of CAD: CCTA versus usual care (2 RCTs,^{18, 20} 1 prospective observational^{21, 22}), CCTA versus various functional testing (1 RCT),²³ and SPECT versus exercise ECG (2 RCTs).^{19, 24}

CCTA Versus Usual Care

- In intermediate-risk patients presenting to the ED, there was low strength of evidence from two fair-quality trials (N=1111) that patients in the CCTA and usual care groups had similar mortality (≤ 30 days: 0% in both groups), MI (index ED visit: 2.3% vs. 3.6%; 28 days: 0.2% vs. 0.8%), any revascularization (index ED visit: 7.2% vs. 5.6%), PCI (index ED visit: 5% vs. 3%; 28 days: 0.6% in both groups), CABG (index ED visit: 1% in both groups; 28 days: 0% in both groups), additional testing (28 days: SPECT [1.6% vs. 1.8%], stress echocardiography [0% in both groups], or exercise treadmill testing [2% vs. 3%]) at the index ED visit and through 28 to 30 days. ICA referral was also similar at the index ED visit (13.8% vs. 11.2%, pooled RD 3, 95% CI 0 to 7 per 100 patients, $I^2=0\%$) and after the index visit through 28 days (1.0% vs. 0.8%) (low strength of evidence).

SPECT Versus Exercise ECG

- In 824 intermediate-risk women (setting not reported) groups were similar with respect to mortality (1.0% vs. 0.5%), ICA referral (6% in both groups), revascularization (2.0% vs. 1.0%), and hospitalization for chest pain (3.9% vs. 3.1%) through 24 months, based on one fair-quality trial (low strength of evidence). However, moderate strength of evidence from this trial suggests that SPECT is associated with less additional noninvasive testing than exercise ECG (9.4% vs. 18.6%; RD -9, 95% CI -14 to -4 per 100 people). Among those randomized to exercise ECG, the frequency of cross over to SPECT (counts as use of additional test) was 8, 25, and 43 percent respectively for women who had normal, indeterminate, and abnormal ECG results. Of those randomized to SPECT, this test was repeated in 9, 8, and 15 percent of women with normal, mildly abnormal, and moderately to severely abnormal results.
- A second fair-quality trial reported that in a subgroup of 280 intermediate-risk outpatients, SPECT was associated with less referral to ICA (10.6% vs. 43.1%, RD -32, 95% CI -43 to -22 per 100 people) (low strength of evidence) and additional stress testing (0% vs. 38%, RD -38, 95% CI -48 to -29 per 100 people) (low strength of evidence) through a mean of 22 months of followup.
- Differences in patient characteristics between the two trial may partially explain differences in findings; One trial was comprised of women with a mean age of 63 years who were able to perform ≥ 5 METS on the Duke Activity Status Index. Findings from the other trial are based on subanalysis of intermediate risk patients from a general population of >50 percent men with mean age of 59 years old with any activity ability.

CCTA Versus Functional testing

- In a good-quality trial of 10,003 intermediate-risk (mean $53\% \pm 21\%$, combined Diamond and Forrester and Coronary Artery Surgery Study risk score for likelihood of

obstructive CAD) outpatients, moderate strength evidence suggests that there is no difference between groups in all-cause mortality (12 months: 0.42% vs. 0.64%; median 25 months: 1.48% vs. 1.50%), nonfatal MI (12 months: 0.36% vs. 0.54%; median 25 months: 0.60% vs. 0.80%), or cardiac hospitalizations (median 25 months: 1.22% vs. 0.92%). There was high strength of evidence that CCTA was associated with more ICA referrals (12.19% vs. 8.11%, RD 4.08, 95% CI 2.90 to 5.26 per 100 people) and revascularizations (6.22% vs. 3.16%, RD 3.07, 95% CI 2.24 to 3.90 per 100 people) (including CABG and PCI evaluated separately) through 90 days. Major procedural complications were rare and similar between groups (procedural stroke [0.02% vs. 0.04%]; major bleeding [0.1% in both groups]; no cases of anaphylaxis or renal failure requiring dialysis) (moderate strength of evidence).

Low To Intermediate Pretest Risk of CAD

A total of seven comparative studies were identified in populations with low to intermediate pretest risk of CAD: CCTA versus usual care (2 RCTs)^{25, 26}, SPECT (2 RCTs,^{27, 28} 1 retrospective observational²⁹), and exercise ECG (1 RCT³⁰, 1 retrospective observational³¹).

CCTA Versus Usual Care

- In a fair-quality trial of 1370 low- to intermediate-risk (TIMI risk score 0 [51%], 1 [36%], and ≥ 2 [13%]) patients presenting to the ED, there is low strength of evidence showing no difference between groups in mortality through 1 month (0% in both groups) or MI diagnosis at the index ED visit (1.0% vs. 0.9%) and through 1 month (1.1% in both groups). Moderate strength of evidence from the same trial suggests that CCTA patients were less likely to be hospitalized at the index visit (50% vs. 77%, RD -26.8, 95% CI -31.9 to -21.8 per 100 people) but cardiac-related hospitalizations through 1 month were similar (3% vs. 2%). The CCTA groups were less likely to undergo additional testing at the index visit (13.7% vs. 57.8%, RD -44.1, 95% CI -49.2 to -39.1 per 100 people), through 1 month (23.1% vs. 66.4%, RD -43.3, 95% CI -48.4 to -38.1 per 100 people) in the same trial (moderate strength of evidence), or through 3 months (33% vs. 60%, RD -27, 95% CI -51 to -2) based on one poor-quality trial of 60 patients (risk scores not reported) (low strength of evidence). While ICA referrals were similar for the groups at the index ED visit (4.1% vs. 3.9%, 1 trial, N=1392) and through 1- to 3-months followup in 2 trials (N=1452) (pooled 5.2% vs. 4.7%, RD 1, 95% CI -1 to 3 per 100 people), there were slightly more revascularization procedures in the CCTA group at the index visit in the larger trial (2.5% vs. 0.9%, RD 1.7, 95% CI 0.3 to 3.0 per 100 people) but revascularization frequency was similar through the followup period across both trials (pooled, 2.7% vs. 1.2%, RD 1, 95% CI 0 to 3 per 100 people) (low strength of evidence).

CCTA Versus Exercise ECG

- Based on one fair-quality trial of 562 low- to intermediate-risk ED patients, there was low strength of evidence that differences were not found in mortality through 12 months (0.6% vs. 0.4%) or in diagnosis of MI at the index ED visit (1.9% vs. 1.7%) and through one month (no additional cases). The 12-month rate of referral to ICA (9.0% vs. 2.3%, RD 4.8, 95% CI 0.8 to 8.9 per 100 patients) and revascularization (4.3% vs. 1.3%, RD 3.1, 95% CI 0.5 to 5.7 per 100 patients) was significantly greater following CCTA than exercise ECG (low strength of evidence).

CCTA Versus SPECT

- In low- to intermediate-risk (median TIMI score 1.0) patients presenting to the ED, there is low strength of evidence from two trials (N=952; one good- and one fair-quality) that no difference was found through 6 months in mortality (0% in both groups). There was moderate strength of evidence that there was no difference in MI (diagnosis at index ED visit, 0.3% vs. 1.5%, RD -1.2%, 95% CI -2.6% to 0.19%; 6 months: 0% in both groups) as reported by both RCTs, or cardiac-related hospitalizations (0% in both groups) in one good-quality RCT. Together, the trials of ED patients reported that ICA referrals were similar at both the index ED test (7.6% vs. 5.5%, pooled RD 4, 95% CI -4 to 11 per 100, $I^2=71.7%$) and through 6 months (0.7% vs. 1.3%, pooled RD -1, 95% CI -5 to 3 per 100, $I^2=71.1%$) (low strength of evidence). Additional noninvasive testing was more common following CCTA at the index visit (the larger, good-quality trial reported 10.2% vs. 0.9% for SPECT [RD 9.4, 95% CI 6.1 to 12.7 per 100 patients] and the smaller, fair-quality trial reported 24% vs. 0% for SPECT [RD 24 per 100 people, $p<0.001$]) (high strength of evidence from two trials); use of additional noninvasive testing through 6 months was similar (1% vs. 3%) (low strength of evidence from one trial). Moderate strength of evidence from both trials of ED patients suggests similar referral for revascularization, including PCI and CABG evaluated separately, at the index visit (3.9% vs. 2.1%) and through 6 months (0.5% vs. 0%).

Intermediate To High Pretest Risk of CAD

A total of two comparative studies (in 3 publications) were identified in populations with intermediate to high pretest risk of CAD: PET versus SPECT (1 prospective observational)^{32, 33} and CCTA versus SPECT (1 RCT).³⁴

CCTA Versus SPECT

- In intermediate- to high-risk patients, there was insufficient strength of evidence from one small, poor-quality trial of 180 outpatients (65% intermediate and 29% high risk; mean Framingham risk estimate 18.7) with a mean of 1.8 months followup that there were no deaths or MIs found. Strength of evidence was low that cardiac hospitalizations occurred similarly between groups (12% vs. 11%). CCTA was associated with more revascularizations (8% vs. 1%, RD 6.6%, 95% CI, 0.7% to 12.5%), as well as slightly more ICA referrals (13% vs. 8%, RD 5, 95% CI -4 to 14 per 100, $p=NS$) and slightly but not significantly less noninvasive cardiac imaging tests (3% vs. 10%, RD -7, 95% CI -14 to 0.4 per 100 people) through the same followup period (low strength of evidence).

High Pretest Risk of CAD

A total of two studies were identified in populations with high pretest risk of CAD: CCTA versus usual care (1 RCT)¹⁸ and SPECT versus exercise ECG (1 RCT).¹⁹ Evidence was based on subgroup analyses and was insufficient for all outcomes.

CCTA Versus Usual Care

- In a small subgroup of 56 high-risk patients presenting to the ED, there was insufficient evidence from one small, fair-quality trial to draw conclusions regarding 1-month mortality between groups (0% in both groups), hospitalization for acute coronary

syndrome (57% vs. 64%, RD -7, 95% CI -33 to 18 per 100, p=NS), ICA referral (75% vs. 93%, RD -18, 95% CI -37 to 0.8, p=0.07), and revascularization(43% vs. 50%, RD -7, 95% CI -33 to 19 per 100, p=NS).

SPECT Versus Exercise ECG

- In a subgroup of 106 high-risk outpatients, there was insufficient evidence that ICA referral was less common in SPECT compared with the exercise ECG group through a mean of 22 months (44% vs. 85%, RD -41, 95% CI -58 to -24 per 100) in one fair-quality trial; data also suggests that additional noninvasive imaging following SPECT may be less common (0% vs. 5%, RD -5, 95% CI -10 to 1 per 100), though the sample size was too small to reach statistical significance (insufficient strength of evidence).

Mixed Population: Pretest Risk Not Reported or Results Not Stratified by Risk

A total of nine comparative studies were identified in populations with mixed pretest risk of CAD or for which risk was not reported (one administrative database study reported outcomes for six different test comparisons): CCTA versus usual care (1 RCT),¹⁸ exercise ECG (1 RCT,³⁵ 1 administrative database³⁶), SPECT (1 prospective registry,³⁷ 1 administrative database³⁸), nuclear MPI (1 prospective observational,³⁹ 1 administrative database³⁶), and stress echocardiography (1 administrative database)³⁶; SPECT versus exercise ECG (1 RCT,¹⁹ 1 administrative database³⁶); and stress echocardiography versus exercise ECG (1 RCT,⁴⁰ 1 prospective observational,⁴¹ 1 administrative database³⁶) and SPECT (1 administrative database).³⁶

CCTA versus Usual Care

- In a fair-quality trial of 266 patients presenting to the ED and not stratified by risk (low 37%, intermediate 42%, high 21%), there was low strength of evidence that a difference was not found in 1-month MI (0% vs. 0.8%) or contrast-induced nephropathy (0% in both groups).

SPECT Versus Exercise ECG

- In outpatients not stratified by risk (low 16%, intermediate 61%, high 23%), there was low strength of evidence from one fair-quality trial of 457 patients that a difference was not found between groups in all-cause mortality (0.8% vs. 0.9%) or MI (0% vs. 0.5%) through a mean of 22 months, while SPECT was associated with fewer revascularizations than exercise ECG (10.8% vs. 17.9%, RD -7.1, 95% CI -13.6 to -0.6 per 100).

Exercise ECG Versus Nuclear MPI

- Low strength of evidence from a large, fair-quality administrative database of Medicare outpatients (N=193,406) suggested that 6-month mortality was similar between groups (0.78% vs. 1.28%, adjusted OR 0.93, 95% CI 0.83 to 1.04). Patients who underwent exercise ECG were less likely to undergo ICA through 6 months than those who were tested with MPI (9.04% vs. 12.13%, adjusted OR 0.72, 95% CI 0.70 to 0.75); revascularization (including CABG and PCI evaluated separately) was performed

similarly between groups (4.31% vs. 4.59%, respectively; adjusted OR 0.90, 95% CI 0.85 to 0.94) (low strength of evidence for both).

Stress Echocardiography Versus Nuclear MPI

- Low strength of evidence from a large, fair-quality administrative database of Medicare outpatients (N=212,947) suggested that 6-month mortality was similar between groups (0.95% vs. 1.28%, adjusted OR 1.00, 95% CI 0.90 to 1.10). Through 6 months, ICA referral was statistically less frequent in the stress echo group (9.50% vs. 12.13%; adjusted OR 0.78, 95% CI 0.76 to 0.81), while additional noninvasive testing was slightly more common in this group (5.57% vs. 3.22%; adjusted OR 1.92, 95% CI 1.83 to 2.0) (low strength of evidence). There were no apparent clinical differences between groups in referral for revascularization (4.22% vs. 4.59%, adjusted OR 0.93, 95% CI 0.88 to 0.98) (including CABG and PCI evaluated separately) (low strength of evidence).

CCTA Versus Exercise ECG

- One fair-quality trial of 500 ED patients not stratified by risk (low 43%, intermediate 24%, high 34%) with 12 months of followup found low-strength evidence that a difference between groups was not found in all-cause mortality (0.4% in both groups) or MI (0.41% vs. 0.82%), while there was moderate-strength evidence that cardiac-related hospitalizations were less common in the CCTA group (0.8% vs. 6.9%, RD -6.1, 95% CI -9.5 to -2.7 per 100). CCTA was associated with more ICAs (27.2% vs. 20.8%; RD 6.3, 95% CI -1.2 to 13.9 per 100 p=0.1011) and more revascularizations (15.2% vs. 7.7%, RD 7.5, 95% CI 1.9 to 13.0 per 100; including PCI [11.9% vs. 4.9%, RD 7, 95% CI 2 to 12 per 100]), though CABG was utilized similarly between groups (3.3% vs. 2.9%) (low strength of evidence).

CCTA Versus Nuclear MPI

- One large, fair-quality administrative database study of 141,163 mixed risk-level Medicare outpatients provided low-strength evidence that all-cause mortality was similar through 6 months (1.05% vs. 1.28%). CCTA patients were more likely to undergo ICA (22.94% vs. 12.13%, adjusted OR 2.19, 95% CI 2.08 to 2.32), additional noninvasive testing (4.98% vs. 3.22%, adjusted OR 1.52, 95% CI 1.37 to 1.69), and revascularization (11.41% vs. 4.59%, adjusted OR 2.76, 95% CI 2.56 to 2.98) (including PCI and CABG evaluated separately) through 6 months (low strength of evidence).
- One fair-quality registry study of 1856 patients provided low-strength evidence that revascularization was more common following CCTA through a median of 1.42 years (% NR, adjusted OR 1.62, 95% CI 1.20 to 2.18); the setting was not reported.

Discussion

Key Findings and Strength of Evidence

Evidence to determine the comparative effectiveness and safety of different noninvasive testing strategies for coronary artery disease (CAD) is limited. While there is a robust body of literature on the diagnostic performance of these tests based on traditional measures of test accuracy (e.g., sensitivity, specificity), only a small number of studies were identified that

evaluated the impact of noninvasive testing on clinical outcomes measures in the population of interest for this report. The key findings and strength of evidence for the outcomes identified as being most clinically important are summarized in Tables 7–14 in the Results section; factors used to determine the overall strength of evidence are summarized in Appendix J.

A total of 22 comparative studies that evaluated the impact of noninvasive testing on clinical outcomes and/or clinical management outcomes in the population of interest for this report form the basis of this review, including 13 randomized controlled trials (RCTs) (2 good quality, 8 fair quality and 3 poor quality),^{18-20, 23-28, 30, 34, 35, 40} nine comparative observational studies (6 fair quality, 3 poor quality).^{21, 22, 29, 31-33, 36-39, 41} Common methodological shortcomings in the RCTs included unclear description of randomization sequence and/or test allocation and lack of blinded outcomes assessment. In the observational studies, lack of controlling for confounding and/or blinding of outcomes assessment were common methodological shortcomings. The comparative studies served as the basis of the report and were stratified based on pretest risk, test type (anatomic or functional), and setting. For most outcomes reported in trials, the strength of evidence was rated as low (meaning that our confidence in the estimates of effect is low) based on concerns related to precision and study limitations. However, there were some outcomes reported by trials for which the strength of evidence was found to be moderate or high. For the majority of outcomes reported by comparative observational studies, the strength of evidence was found to be insufficient due to study limitations, although some outcomes were graded as low strength of evidence when the estimates were considered to be at low risk for imprecision and confounding was controlled. Eight RCTs and one observational study were conducted in ED settings or specialized chest pain clinics³⁵ and compared coronary computed tomography (CCTA) with functional testing^{27, 28, 30, 35} or usual care.^{18, 20-22, 25, 26} In these studies, most of the available data was reported for the index ED visit, and with the exception of two trials reporting 12 month followup, the maximum followup in ED studies was 6 months. The remaining five trials^{19, 23, 24, 34, 40} and 13 comparative observational studies were conducted in outpatient, various, or unspecified settings; in general, these studies had longer followup periods, which ranged from a mean of 55 days to 30 months. Pretest risk could not be standardized across studies and was variably determined and defined across studies. Thus, categories of pretest risk below are based on how authors defined it.

Clinical Outcomes

There was no clear difference in MI or all-cause mortality between different testing strategies across settings and pretest risk groups that included intermediate pretest risk patients based on low to moderate strength of evidence from eight trials. The definition of intermediate pretest risk was broad. The frequency of all-cause mortality was low across studies in all settings. In trials enrolling outpatients, all-cause mortality frequency ranged from 0 to 1.5 percent for a variety of noninvasive testing strategies, and the frequency in trials in the ED setting past the initial index visit ranged from 0 to 1.08 percent, across a variety of noninvasive testing or usual care strategies with no statistical difference between any groups. Similarly, the frequency of MI was low, ranging from 0 to 0.8 percent in outpatient (up to median of 25 months) studies and 0 to 3 percent (up to 12 months) in ED settings with no statistical differences between groups. The strongest evidence came from three trials, one that compared CCTA with functional testing in an outpatient setting,²³ and two that compared CCTA with single photon emission computed tomography (SPECT) in an ED setting.^{27, 28} For the trial of CCTA versus functional testing, which was also the largest trial (N =10,003), there were no differences in all-cause mortality

between groups through 12 months (0.42% vs. 0.64%) or at median of 25 months (1.48% vs. 1.50%) followup or in nonfatal MI at 12 months (0.36% vs. 0.54%, risk difference [RD] -0.18, 95% confidence interval [CI] -0.44 to 0.08 per 100 people) or median of 25 months (0.60% vs. 0.80%, RD -0.20, 95% CI -0.53 to 0.13 per 100 people)²³; strength of was moderate for both outcomes. Across the two trials comparing CCTA with SPECT in an ED setting, there was low strength of evidence that no difference was found between tests for mortality or MI; there were no deaths or MIs reported through a mean of 6 months past the initial ED visit.^{27, 28} Across the remaining trials, the strength of evidence was also low that no difference was found between tests due to lack of precision and study limitations. Higher-quality observational studies (i.e., those that controlled for confounding) supported these findings. No conclusions can be drawn regarding the impact of testing on clinical outcomes for patients at low risk or high risk (without ECG changes or troponin elevation or other characteristics of ACS) as only subanalyses of less than 100 patients were available.

Several factors may contribute to finding no statistical differences between tests on clinical outcomes. Given the low incidence of mortality and MI in the across studies noted above, sample sizes in even the largest trials may have been too small to detect differences between tests. The low incidence suggests that study populations may generally have been at the lower end of the intermediate pretest risk range. Improvements in medical therapy in the past few decades, including use of statins, may contribute to the low incidence of these outcomes. An additional consideration is the possibility that differences in the true sensitivity between tests to detect treatable CAD or ability to identify high risk disease are not large. Small differences in sensitivity may have little impact on the probability of disease when the pretest probability is low. Even if two tests do not have the same sensitivity, the lack of difference in the occurrence of outcome events in most studies between persons who were assigned to receive different tests could be due to either the lack of efficacy of treatments administered to test-positive persons; or the lack of difference in the receipt of effective treatments between test-positive and test-negative persons. Given that studies do not present data on treatments administered to individual study participants (or how testing directed those decisions), we cannot distinguish between these alternatives. Furthermore, information on posttest risk stratification or treatment based on such stratification was not reported in most studies. Information on clinical decisions and outcomes based on whether tests were positive, negative or indeterminate was not described in most comparative studies. It is possible that over- or under-treatment may contribute to similarity in clinical findings. Length of followup may also impact the findings of no difference in clinical outcomes. Two larger trials in outpatient settings (SPECT vs. stress electrocardiography [ECG]²⁴ and CCTA vs. functional testing²³) followed patients for two or more years. Most studies in the ED setting did not provide data beyond 6 months of the ED visit; testing is only able to affect clinical events after the index visit, consequently there is insufficient evidence to draw conclusions regarding clinical outcomes longer term.

Referral For Invasive Coronary Angiography

There was some variability in conclusions regarding invasive coronary angiography (ICA) referral following noninvasive testing. In most studies, ICA was most common following CCTA compared with various functional tests. The strongest evidence came from one good quality trial that compared CCTA with functional testing in outpatients, which found that ICA was significantly more common in the CCTA group than the functional testing group by 90 days (12.19% vs. 8.11%, RD 4.08, 95% CI 2.90 to 5.26 per 100 people) (high strength of evidence).

Interestingly, fewer catheterizations in the CCTA group showed no obstructive CAD (3.4% vs. 4.3%),²³ perhaps due to a lower false positive rate with CCTA. Otherwise, the strength of the quality of evidence regarding ICA referral was low across the remaining trials. Two fair quality trials comparing CCTA with exercise ECG suggest that ICA referral is more common following CCTA up to 12 months following initial ED visit with RD 4.8 (95% CI 0.8 to 8.9 per 100 people) in one trial of low to intermediate risk patients and RD 6.3 (95% CI -1.2 to 13.9 per 100 people) in the other trial of mixed risk; statistical significance was not reached and strength of evidence was low due to study limitations and lack of precision. A large administrative data study in Medicare patients also found that ICA was significantly more common following CCTA compared with nuclear myocardial perfusion imaging (MPI) (22.94% vs. 12.13%, adjusted odds ratio [OR] 2.19, 95% CI 2.08 to 2.32); the strength of evidence was low.³⁶ In contrast, across studies comparing CCTA with usual but there were no statistical difference between testing strategies in any of the trials regardless of pretest risk or setting, however, in the small high risk group from one trial, fewer CCTA patients had ICA at the index visit (RD -18, 95% CI -37 to 0.8, $p=0.0714$); strength of evidence was low. Evidence from observational studies for comparisons of CCTA with other tests was considered insufficient due to study limitations and lack of precision. Regarding comparisons of functional tests, two RCTs^{19, 24} and one large administrative database study³⁶ provided low strength of evidence on ICA referral in outpatient settings. One trial comparing SPECT with exercise ECG in intermediate risk women reported a six percent referral for ICA in each test group by 24 months. However, the other trial making this comparison reported significantly a lower frequency of ICA referral following SPECT in a subgroup of intermediate pretest risk patients (RD -32, 95% CI -43 to -22 per 100 people) as well as in a subgroup of high risk patients (RD -41, 95% CI -58 to -24 per 100 people) by 22 months.¹⁹ This same trial used Bayesian methods to model posttest risk and reported that 86 percent of those with low pretest risk finished with low posttest risk and that those with a normal or low risk test in either arm did not receive ICA; 3 percent and 38 percent in the intermediate and high posttest risk groups had ICA following SPECT compared with 13 percent and 85 percent in these respective groups following exercise ECG. As such modeling is not a standard approach to posttest risk assessment, the generalizability of these results is not clear. The administrative database study of Medicare patients reported that compared with nuclear MPI, ICA referral was lower following exercise ECG (OR 0.72, 95% CI 0.70 to 0.75) and stress echocardiography (OR 0.78, 95% CI 0.76 to 0.81)³⁶ (low strength of evidence). Evidence from the remaining observational studies was considered insufficient.

None of the studies provided analysis or explicit information regarding unnecessary treatment or testing.

Revascularization

Findings were inconsistent across diagnostic strategies with regard to revascularization referral. There was high strength of evidence from one large trial that any revascularization was more common following CCTA compared with functional testing within 90 days (RD 3.07, 95% CI 2.24 to 3.90 per 100 patients); the same was true for percutaneous coronary intervention (PCI) specifically (RD 2.4, 95% CI 1.7 to 3.1 per 100 patients)²³ (high strength of evidence). Revascularization was also more common 6 to 12 months following CCTA compared with exercise ECG across two studies (1 RCT, 1 observational)^{35, 36} of mixed risk ED patients (low strength of evidence), as well as across two observational studies comparing CCTA with nuclear MPI^{36, 39} in outpatient setting up to 1.4 years (low strength of evidence). By contrast,

revascularization was similar for CCTA and SPECT (pooled RD 2 per 100, 95% CI 0 to 4 per 100 patients) at the index ED visit and at 6 months (pooled RD 0, 95% CI 0 to 1 per 100 patients) across two trials (moderate strength of evidence).^{27, 28} PCI and CABG frequencies in these trials were also similar between tests; strength of evidence was moderate. Further, there was low strength of evidence of no statistical differences in revascularization frequency between CCTA and usual care at the index visit or at 1 to 3 months followup based on data from four trials.^{18, 20, 25, 26} Evidence comparing functional tests was inconsistent, with one small trial reporting fewer revascularizations following SPECT than exercise ECG (RD -7.1, 95% CI -13.6 to -0.6 per 100)¹⁹ (low strength of evidence), and one large Medicare administrative database study reporting a similar frequency of revascularization (including PCI and CABG) for exercise ECG (4.31%, vs. 4.59%) and stress echocardiography (4.22% vs. 4.59) compared with nuclear MPI (low strength of evidence). For the latter study, although the difference between groups were statistically significant for both comparators, they may not be clinically significant. Studies did not describe posttest reclassification of risk or decisionmaking for treatment.

Additional Noninvasive Testing

Additional noninvasive testing, which impacts the cost and efficiency of care, was common in most studies. In the ED setting, there was high strength of evidence from two trials of low to intermediate risk patients that additional noninvasive testing was significantly more common following CCTA compared with SPECT at the index visit (RD for largest trial 9.4, 95% CI 6.1 to 12.7 per 100 patients).^{27, 28} In the same setting, there was moderately strong evidence that CCTA was associated with less frequent noninvasive testing compared with usual care at the index visit in one trial²⁵ and compared with exercise ECG through 12 months (past the index ED visit)³⁵ in another trial. In intermediate risk patients additional testing frequency following CCTA was similar to usual care up to 1 month past ED visit in one trial (low strength of evidence), possibly because many in the usual care group also received noninvasive imaging.²⁰ In outpatient settings, the strength of evidence was moderate that SPECT was associated with significantly less additional noninvasive testing compared with exercise ECG through 22 months based on one large trial of intermediate risk women (RD -9, 95% CI -14 to -4 per 100)²⁴ as well as a from a subgroup of intermediate risk patients in another trial (RD -38, 95% CI -48 to -29 per 100)¹⁹ likely indicating greater clinician confidence when stress is paired with imaging based on general understanding from accuracy studies that positive and negative predictive values are better for SPECT. In the Medicare administrative database study, both CCTA and stress echocardiography were associated with significantly higher frequency of additional noninvasive testing compared with nuclear MPI (OR 1.52, 95% CI, 1.37 to 1.69 and 1.92, 95% CI 1.83 to 2.0, respectively) but strength of evidence is low. Studies generally did not describe posttest reclassification of risk or decisionmaking for related further testing.

Hospitalization

Cardiovascular-related hospitalizations varied somewhat across pretest risk groups across studies. There was moderate strength evidence from one large trial of low to intermediate risk ED patients that the CCTA group was significantly less likely than was the usual care group to be hospitalized or admitted for observation at the index visit (RD -26.8, 95% CI -31.9 to -21.8 per 100), but that after this visit through one month, there was no difference between (3% for CCTA vs. 2% for usual care).²⁵ Low strength of evidence from another large trial of intermediate risk ED patients suggested that there were fewer hospitalizations following CCTA compared

with usual care at the index visit (RD -33, 95% CI -39 to -28 per 100 patients).²⁰ These data imply clinician confidence in the negative predictive value of the anatomic test, yet there is a predisposition of patients to return with unexplained symptoms that can be from a variety of other causes of chest pain such including vasospasm and microvascular dysfunction. By contrast, no statistical differences between CCTA and usual care were identified for acute coronary syndrome hospitalization at the index visit based on subgroups of low or high risk patients in one trial,¹⁸ but strength of evidence was low. There was moderate strength of evidence that there was no difference in cardiovascular hospitalizations between CCTA and functional testing groups in low to intermediate pretest risk ED patients within 6 months (0% in both groups) based on one trial,²⁷ and through 30 months based on one observational study²⁹ that compared CCTA with SPECT. Moderate strength of evidence suggested that hospitalization for cardiac causes occurred less frequently in the CCTA group compared with the exercise ECG group (RD -6.1, 95% CI -9.5 to -2.7 per 100 people) through 12 months in another trial of mixed pretest risk patients presenting to specialized chest pain clinics.³⁵ Two trials conducted in outpatient settings reported no differences in cardiac-related hospitalizations between groups. The strongest evidence came from the large trial comparing CCTA with functional testing, which reported no differences at a median of 25 months (RD -0.30, 95% CI -0.10 to 0.71 per 100 people)²³; strength of evidence was moderate. The trial of SPECT versus exercise ECG in women also found no difference between groups; strength of evidence was low.²⁴

Special Populations

With regard to evaluation of special populations, one high trial comparing CCTA with functional testing, reported that none of the prespecified subgroups modified the primary composite outcome [all-cause death, nonfatal MI, hospitalization for unstable angina, or a major procedural complication (stroke, major bleeding, anaphylaxis, renal failure requiring dialysis)], with results across subgroups consistent with those for the entire study population. Subgroups examined included age sex, race, pretest risk assessment, CAD equivalence, and pretest probability of CAD.²³ None of the other studies identified evaluated differential effectiveness or safety. As noted above, one fair quality trial of exercise SPECT with exercise ECG in women found no differences between tests for mortality, ICA referral, revascularization, or hospitalization but did report a significantly lower use of additional noninvasive testing following SPECT.²⁴ The strength of evidence was moderate for additional testing and low for other outcomes. An additional small poor quality RCT in women compared stress echocardiography with exercise ECG reported similar frequency of a composite outcome which included cardiac death, MI, unstable angina, or coronary angiography demonstrating 50% or more luminal narrowing (7.7% vs. 7.4%),⁴⁰ however the strength of evidence was insufficient due to high risk of bias, lack of precision and unknown consistency. Also as noted above, a large, fair quality administrative data study in the Medicare population was identified.³⁶ Consistent with findings in other studies, there were no differences in adjusted effect estimates for all-cause mortality for the comparisons of nuclear MPI with stress echocardiography, exercise ECG, or CCTA. CCTA was significantly associated with increased referral for ICA and revascularization, (particularly PCI) and use of additional noninvasive testing compared with nuclear MPI; strength of evidence was low for these outcomes and comparisons.

Harms and Consequences of Testing

Harms of testing were rarely reported and details comparing harms for test were sparse with many studies stating that no harms were observed without providing further detail; 16 of the 27 comparative studies made no mention of evaluation of harms. There are no compelling safety outcomes data that can be used to recommend one approach versus another and strength of evidence was low or insufficient. No differences in major procedural complications were identified in the trial comparing CCTA with functional imaging although mild contrast reactions were significantly more common in the CCTA group than in the functional testing group (moderate strength of evidence).²³ No differences between CCTA and usual care in bradyarrhythmia in one trial²⁵ or periprocedural complications in another²⁰ (low strength of evidence for all). A third trial reported that there was no clinical or laboratory evidence of contrast-induced nephropathy in either the CCTA or usual care group.¹⁸ One observational study reported incidental findings requiring further investigation in 7.1% of those receiving CCTA (insufficient evidence).²⁹ Evidence from observational studies regarding test related harms and impact of incidental findings following CCTA was insufficient to draw conclusions.

A important patient safety concern is exposure to low to moderate levels of ionizing radiation related to noninvasive testing that add to cumulative lifetime radiation exposure. To the extent that noninvasive tests for CAD reduce the need for conventional angiography, cumulative exposure might be reduced. To the extent that they result in the need for additional testing, it may be increased. The true attributable risk from radiation-based diagnostic tests cannot be determined. Some experts consider the potential for harm from radiation exposure (either deterministic or stochastic) to be clinically significant particularly given that patients may be likely to have additional tests using radiation over many years. Estimates of radiation exposure from included studies are provided in Appendix G (Table G4) and the introduction provides contextual information on radiation exposure ranges for testing. Radiation exposure from included studies for initial testing strategies ranged from 3.8 to 17 mSv for CCTA and 10.5 to 38 for SPECT. One study reported a mean of 4.0 mSv for PET³³ and another study²⁰ reported a mean of 4.7 mSv for usual care. Consideration of cumulative radiation exposure related to downstream testing and intervention is important when discussing the benefits and consequences of the different noninvasive tests and their contribution to life-time radiation exposure. Higher mean cumulative radiation accounting for additional testing was seen in single trials following CCTA compared with usual care (14.3 ± 10.9 vs. 5.3 ± 9.6 mSv)²⁰ and functional testing (12.0 ± 8.5 vs. 10.1 ± 9.0 mSv)²³. One study reported higher cumulative exposure for following CCTA versus SPECT in patients referred for ICA (medians, interquartile ranges, 15.2 mSv, 12.7 to 17.1 vs. 10.8 mSv, 10.2 to 11.7).³⁷ By contrast, another trial reported lower cumulative exposure for additional testing following CCTA versus SPECT (medians, interquartile ranges 7.3 mSv, 5.1 to 13.7 vs. 13.3 mSv, 13.1 to 38.0).³⁴ One observational study of CCTA and exercise ECG reported higher exposure for index and downstream testing for CCTA for those who tested negative as well as those who tested positive or whose tests were inconclusive, however among those who tested positive who had revascularization, mean cumulative exposure was slightly higher in the ECG group (28 vs. 32 mSv).³¹ Consideration of patient preferences with regard to the impact of radiation exposure should be part of shared decision making around noninvasive testing.

Findings in Relationship to What is Already Known

Few prior reviews have evaluated the impact of noninvasive testing on clinical and management outcomes. Systematic reviews and studies on noninvasive testing for coronary

artery disease identified from our search focused on traditional measures of test performance (e.g., sensitivity, specificity) compared with ICA and generally did not directly compare the effectiveness and safety of different modalities with regard to impact on clinical outcomes specifically in the population of interest in this report. Consistent with this review, prior systematic reviews^{42,43} have reported few or no comparative studies evaluating the impact of noninvasive tests on clinical outcomes, decisionmaking, or use of additional testing and note that harms are rarely reported; relevant studies from these reports were included in this systematic review. The recent Agency for Healthcare Research and Quality (AHRQ) report on noninvasive testing in women reported that there was insufficient evidence from three studies that treatment decisionmaking and clinical outcomes were impacted by noninvasive testing.⁴⁴ Consistent with our report, there were no differences in clinical events or hospitalization in studies comparing noninvasive tests. They also concluded that studies were underpowered to detect clinical outcomes.

Applicability

There are a number of factors that impact the applicability of this report's findings.

Patients

Eight of the 13 trials identified were in patients presenting to the ED with CAD symptoms, however the largest trial was in an outpatient setting. Patients presenting to the ED represent a broad spectrum of pretest risk probabilities including those at low or intermediate risk as well as those at high risk for CAD. The severity, newness and duration of symptoms may differ from those seen in outpatient settings, who generally present with more mild to moderate symptoms. Definitions of pretest risk varied across included studies and some did not report or stratify by pretest risk, making it difficult to fully evaluate results based on pretest risk across settings. It is likely that the patients enrolled in the included studies are representative of those in the broad range of clinical practice.

Interventions and Comparators

The evidence may be skewed toward newer testing modalities and studies of established tests may not reflect current technology and diagnostic performance. CCTA was the most common noninvasive test assessed, accounting for 48% of included studies. This may be because CCTA is a newer modality and thus is compared with established tests, such as stress echocardiography and myocardial perfusion imaging. Few studies comparing different types of functional testing, particularly between established functional tests such as stress echocardiography, exercise ECG and nuclear stress testing were identified. A recent systematic review suggests that over the past two decades, substantial decline was seen in investigations related to echocardiography and nuclear cardiology compared with marked increase in cardiac CT imaging studies.⁴⁵ Input from clinical team members and the Technical Expert Panel (TEP) suggests that there is substantial variation in clinical practice with regard to which test may be ordered as an initial test based on patient presentation, testing availability and clinical perspective. Thus, it is not clear to what extent CCTA may or may not be the initial noninvasive test for first-line evaluation of symptomatic patients without known CAD after a resting ECG and therefore impact the applicability of this report. None of the included studies included a "no testing" arm. To the extent that clinical decision making is done based on clinical evaluation and judgment without

testing findings in this report may be less applicable to settings where testing is not routinely done.

Outcomes

Findings related to rare outcomes of death, MI or hospitalization may not be fully applicable to broader clinical populations in part due to small study sizes and inability to fully characterize such outcomes, particularly over the longer term. Moreover, the impact of a negative test or the treatment downstream from a positive test may extend beyond traditional major adverse coronary events to quality of life, reduction in symptoms, and level of activity. These outcomes have not been examined in the majority of included studies. The majority of trials reported outcome at the time of an index ED visit. The clinical management objectives in an ED setting are somewhat different than in an outpatient setting.

Settings

Most RCTs were conducted in the ED to help determine immediate disposition for discharge or additional evaluation and/or hospitalization. The initial goal is to make a diagnosis for the cause of chest pain in order to inform appropriate treatment and next steps at the index visit; thus, MI reported at the index visit may reflect a test's ability to make the diagnosis for immediate decisionmaking but does not reflect the tests' ability to impact future clinical outcomes. Testing is only able to affect events after the index visit and long term follow up from ED studies was limited. Thus the applicability of findings from ED studies to general outpatient settings over the long term is likely limited.

Implications for Clinical and Policy Decisionmaking

The 2012 American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) guideline states that diagnostic testing is most valuable when the pretest probability of ischemic heart diseases is intermediate (10% to 90%) and provides a range of options for which test may be used in a given scenario however the effectiveness of different modalities with regard to impact on clinical outcomes are not compared.¹⁰ Currently, a variety of tests as the initial (and additional) diagnostic tests for patients at intermediate pretest risk of CAD are employed and there is uncertainty regarding which tests, if any, may be most suitable and beneficial in patients who present with symptoms suggestive of CAD but have no prior history of it. Although several ACCF/AHA Appropriate Use Criteria (AUC) are available, including the 2013 multi-modality imaging AUC,⁴⁶ they do not explicitly compare multiple NIT modalities nor do they make specific recommendations for timing/sequencing of tests or for repeat testing based on pretest risk group.

Low to moderate strength of evidence from eight trials suggested there is no clear difference in MI or all-cause mortality between different testing strategies across settings and pretest risk grouping which included those at intermediate risk; possible contributors to this finding, including lack of power to detect a difference, were previously described. Information from two studies that provided data on low and high pretest risk (without ACS) groups do not provide insight into the best testing strategies in those groups; the strength of evidence was insufficient for the few outcomes reported and no conclusions can be drawn. Across studies that enrolled intermediate-risk groups, no clear benefits of one testing strategy versus another were seen and no clear picture of harms for various tests was available from included studies. One apparent trend uncovered by the review is that tests that evaluate coronary anatomy, such as CT, result in

a greater likelihood of referral for ICA and subsequent intervention than functional tests; however, the strength of evidence varied from high to low depending on the comparator, and the impact on clinical outcomes is not known as most studies do not present data on treatments administered to individual study participants. Thus, it is not clear if the increased referrals were helpful or not with regard to influencing clinical outcomes. Only two studies provided limited information on the overall impact of testing and resulting treatment strategies on patient symptoms and quality of life. No studies that compared testing to an arm that received no testing were identified, so the impact of any of the noninvasive testing pathways over clinical evaluation is not known.

As defined in the ACCF/AHA guidelines, the intermediate pretest group is broad and heterogeneous (10% to 90%) and in the absence of information on posttest risk, the value of the various tests for influencing important management decisions at each end of the spectrum is not clear. Various ACCF appropriate use criteria⁴⁷⁻⁵⁰ and guidelines provide general recommendations for testing and treatment. For example, a 25 year-old woman who is a current smoker with atypical chest pain would have a low pretest risk. Her pretest probability of obstructive coronary artery disease is low. Performance of an imaging cardiac stress test would be considered inappropriate or rarely appropriate⁴⁷; an exercise ECG test could be performed, but would be graded a IIb recommendation.⁴⁸ If this were a 45 year-old woman with history of smoking she would be intermediate risk for obstructive coronary artery disease and it would be appropriate for her physician to order a stress echocardiogram⁴⁷ or similar test.

In general, next steps following a positive result from an initial noninvasive test is in part based on the posttest annual predicted rate of cardiac mortality as described in the 2012 ACCF/AHA guideline: low risk (<1% per year), intermediate risk (1% to 3% per year), or high risk for cardiac mortality (>3% per year).¹⁰ Clinical presentation and test results are both considered in this determination. A positive test can trigger treatment with guideline directed medical care, or if high risk, can precipitate a coronary angiogram and consideration for revascularization. In general, people who would be categorized as being at low risk (test result is negative) or intermediate risk and who do not exhibit characteristics of acute coronary syndrome medical management may be appropriate. In most instances, patients in these categories can be managed without invasive assessment. In the case of the 45 year old woman above, based on a normal exercise echocardiogram then she is reclassified as low risk and predicted to have an annual event rate of cardiac death or nonfatal myocardial infarction of less than 1 percent.⁵⁰ Treatment of high blood pressure and smoking cessation would be appropriate; but further diagnostic evaluation would not be warranted unless there was a change in clinical status. If this patient had an abnormal stress test which was intermediate risk medical therapy for CAD in addition to comorbidities would be appropriate; proceeding to angiogram would be at the discretion of the physician⁴⁹ through a shared decision making process. In patients who are considered to be at high risk based on noninvasive testing and presentation, invasive coronary angiography for further risk stratification and assessment of appropriateness for revascularization may be the next logical steps. In general, indications for revascularization are based on the clinical presentation (acute coronary syndrome or stable angina), the severity of the angina (based on Canadian Cardiovascular Society Classification), the extent of ischemia on noninvasive testing, and the presence or absence of other prognostic factors including congestive heart failure, depressed left ventricular function, and diabetes, the extent of medical therapy, and the extent of anatomic disease.^{51, 52} However, it is considered appropriate for a symptomatic patient with a high pretest probability of obstructive coronary artery disease to undergo stress

imaging for diagnostic or prognostic reasons.⁴⁷ In either case appropriate medical therapy for comorbidities and suspected coronary artery disease with anti-anginal agents in addition to aspirin and statin therapy would be prescribed.

From the included studies, however, it is not clear how posttest risk was assessed, if these or other pathways were followed after the initial test, which test may lead to the most appropriate treatment give the posttest risk or whether the treatments impacted outcomes. While the various ACCF/AHA guidelines an appropriate use criteria provide a range of options for which test may be used in a given scenario and treatment initiated, the effectiveness of different testing modalities leading to appropriate treatment are not compared with regard to impact on clinical outcomes.

In the absence of high strength evidence regarding testing options, including the possibility of not testing, decisions must necessarily be made on the basis of other factors related to the initial test and beyond. The ability of a test to accurately diagnose treatable CAD is important; so too are the costs and consequences beyond the initial test such as followup of false negative results (e.g., tests with high false positive rates in a low pretest risk population) and the costs and consequences of missing significant disease (e.g., dismissal of patients with CAD needing treatment from the ED). The costs and consequences depend to some extent on the role a test plays in the diagnostic work up pathway as well as the availability and convenience of a test. Consequences of testing that need to be considered include those related to patient anxiety and patient quality of life and those related to radiation exposure of the index test as well as potential downstream exposure from additional testing resulting from the initial test and future testing and/or treatment. Consideration of patient preferences, based on their understanding the range of consequences of initial and downstream testing, is an important part of shared decisionmaking for initiating noninvasive testing.

Limitations of the Systematic Review Process

This review has some potential limitations. In keeping with the intent of Key Questions, stratifying by pretest risk may have resulted in fewer studies to pool and leaving single studies for most comparisons. This, combined with substantial heterogeneity in how pretest risk was defined, the time frames over which outcomes were evaluated, and clinical heterogeneity between tests evaluated, resulted in too few studies for head to head meta-analysis for most outcomes, and network meta-analysis was not feasible. Variable reporting on patient symptoms and characteristics related to CAD risk precluded application of a standardized method for calculating or assigning pretest risk across studies. In light of this, test comparisons were evaluated according to pretest risk as specified by authors to discern patterns within and across pretest risk levels and setting to qualitatively synthesize outcomes when pooling was not possible. This resulted in limited ability to truly examine the evidence by pretest risk. Inclusion was restricted to studies published in English; however, this is not likely to have impacted the evidence base as few non-English language studies of potential were seen in the searches. Formal, statistical assessment of reporting and publication bias was not possible; however, we did consult published study protocols and solicited and evaluated Scientific Information Packets. Given the paucity of RCTs, comparative observational studies were included and despite a focus on outcomes in studies that controlled for confounding, there is a possibility that residual confounding influenced reported results, lowering confidence in effect estimates. Comparative studies included may not adequately capture harms safety issues in the population of interest. The focused criteria on inclusion of studies comparing an established first-line test (beyond a

resting ECG) narrowed the review scope substantially, but this focus was intended to provide a clearer approach to addressing the areas of uncertainty described in the introduction. It is possible that older, historical studies outside of our population of interest could provide more detailed information about the safety of various tests, particularly more established tests. There were too few studies of any given comparison to meaningfully evaluate publication bias. Where available, protocols of trials were reviewed to consider the extent to which outcomes were reported selectively and information from Scientific Information Packets requested from stakeholders was evaluated; while overt publication bias was not detected, there is always the possibility it may be present. This review provides a snapshot of currently available evidence on the questions posed. Included studies may not reflect technological advances that have been made in the various testing modalities.

Limitations of the Evidence Base

Important limitations of the evidence base include the paucity of studies that compared the impact of different noninvasive tests on hard clinical outcomes such as mortality and myocardial infarction; few RCTs were available, in particular for comparisons of established functional tests in the population of interest. No trials that included a no testing arm were identified. Methods for assessing pretest risk, defining cardiovascular outcomes, and defining usual care were poorly reported and not standardized. The variable methods for determination and classification of pretest risk across studies and inability to implement a standardized method for assessing pretest risk across studies precluded detailed evaluation of testing strategies by pretest risk level to determine the comparative values of tests for a given pretest risk. The intermediate risk range is broad (10% to 90%). Studies did not provide information on the impact of test results on posttest risk stratification or clinical decision making for treatment or further testing precluding evaluation of the impact of testing in this group. Some studies reported composite cardiovascular outcomes, which can be misleading depending on the effects on the individual components.⁵³ Studies did not evaluate aspects of unnecessary testing. Reporting of harms was suboptimal; 16 of the 27 comparative studies made no mention of evaluation of harms and another three merely stated that there were no adverse events and with the exception of one study, authors reported few details about harms. As mentioned previously, study sample sizes and short-term followup may preclude evaluation of rare events. Studies did not describe the impact of testing on treatment choices. Few studies on PET, CACS and establish tests such as stress echocardiography were identified.

Research Gaps and Recommendations

The gaps in the available evidence are many and include:

- Lack of studies that compare testing and resultant treatment strategies to clinical evaluation (and resulting treatment strategies) without testing. This is particularly important in those at very low or low pretest probability.
- Lack of a standardized approach to determining and reporting pretest risk across studies; variable definitions of pretest risk precluded ability to effectively stratify by pretest risk.
- The large range of pretest likelihoods across studies precluded detailed evaluation of the impact of testing on clinical decision making or outcomes for those that are at the lower end of the range and those at the higher end. Future research should use risk models that further refine the range of pretest probability for those at intermediate risk (e.g., The

Duke Clinical Score) to delineate the impact of testing on clinical decision making at the lower and higher ends of the range. Tools that refine the range may also be clinically useful.

- There is insufficient information from included studies on the comparative impact of tests on posttest risk stratification.
- There is limited high-quality comparative evidence linking established tests with clinical outcomes and decisionmaking in the population of interest by pretest risk, particularly in nonemergent settings and over the longer term. Studies describing outcomes at the index ED visit do not allow conclusions regarding the impact of testing on clinical outcomes.
- No studies evaluated issues of unnecessary testing or treatment.
- There is limited information on the impact of testing on treatment decisions, including those related to use of medical therapy, and downstream testing, including followup of false negative tests and impact of missed disease. It is not clear whether the individuals that would most benefit from a given treatment strategy were referred to those strategies and whether the strategies were effective.
- There is limited evidence on the best testing strategy for posttest risk stratification for discerning which patients may be at highest risk and may benefit most from various treatment strategies.
- There is limited evidence on the impact of testing strategies (including consequences of downstream testing and treatment) on patient-related outcomes such as quality of life and symptom status.

There is a need to enhance the evidence linking testing strategies and clinical pathways to clinical outcomes. Few trials listed on ClinicalTrials.gov appear to be active or pertain to symptomatic patients without known CAD (for details, see Appendix K of full report). To determine optimal testing strategies and roles of tests in different pretest risk groups, several issues should be addressed in future research. First, use of standardized risk models that refine and narrow the currently broad “intermediate” risk group are needed. For example, because healthcare trends to streamline and reduce the cost of care, newer risk models such as the Duke Clinical Score have narrowed the intermediate range and tend to reclassify many of those classified as “intermediate risk” in the Diamond-Forrester model to “low risk”.⁵⁴ Documentation of posttest risk stratification and its impact on clinical management (treatment and referral for additional testing) needed to determine optimal testing strategies and roles of tests in different pretest risk groups. This may facilitate comparison of tests to effectively parse out patients at the highest risk end and those at the lower risk end and evaluation of the impact of management decisions in these groups as they likely will differ. Documentation of management of those who test positive compared to those who test negative and followup of these groups for sufficient time to evaluate clinical outcomes is needed. These factors should be considered for all future comparative studies. RCTs, including pragmatic trials which attend to these issues and have sufficient power to detect differences in clinical outcomes are desirable. Prospective cohort studies that address selection bias and confounding by indication in addition to those related to the issues above have the potential to enhance the evidence base and may be more feasible for some settings. Studies comparing testing to clinical evaluation without testing would provide valuable information on the impact of testing in general and are much needed to help assess the need for testing and possible overuse of testing. Comparative studies (RCTs or prospective cohorts) of functional tests that reflect technological advances as applied to symptomatic patients

without known CAD would update the evidence base. Meta-analysis of patient-level data from existing trials may allow for more specific stratification by pretest probability or specific risk factors. Studies documenting how specifically test results influence decisionmaking regarding further testing and treatment strategies and following patients to evaluate the impact of the testing pathway would provide important insights into the overall impact of testing on long-term outcomes. Future research also needs to incorporate evaluation of patient-centered outcomes.

Conclusions

There were no clear differences between testing strategies across settings with regard to clinical or management outcomes to recommend one strategy over another for any given pretest risk group that included intermediate pretest risk patients. No conclusions regarding low risk patients or those without ACS at high risk are possible. Limited evidence from randomized controlled trials found no clear differences between CCTA versus other strategies in clinical outcomes across risk groups, though anatomic testing may result in a higher frequency of referral for ICA and revascularization. The absence of information on posttest risk stratification and subsequent decision making precluded evaluation of the impact of testing on patient management or outcomes of management. Testing strategies vary in radiation exposure; there is inadequate comparative evidence to make judgments regarding exposure for initial test or downstream testing. Assessment of harms was limited. Future research using more refined, evidence-based definitions of pretest risk coupled with information on posttest risk stratification, its impact on clinical management (treatment and referral for additional testing) and longer term follow up to assess clinical outcomes are needed to determine optimal testing strategies and roles of tests in different pretest risk groups.

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Introduction

Background

Nature and Burden of Coronary Artery Disease

The public health and economic burdens of coronary artery disease (CAD) are substantial. CAD causes one in six deaths in the United States and is the leading cause of death globally.¹ Annually, approximately 635,000 Americans experience a new coronary event, 280,000 will have a recurrent ischemic event, and an additional 150,000 will have a silent first myocardial infarction.² A large proportion of ambulatory health care visits are for evaluation of patients with suspected CAD, with an estimated 1.5 percent of the population presenting to healthcare providers with chest pain every year.³ An estimated \$108.9 billion is spent annually on CAD treatment.⁴ Optimizing the process for assessing these patients presents an opportunity to improve patient outcomes and target health resources to where they can have the most impact.

The most common underlying cause of CAD is atherosclerosis, a disease process in which plaque (which has a complex and varied composition that includes lipids, inflammatory cells, smooth muscle cells, and connective tissue) builds up on artery walls. Plaque formation can result in the partial or complete blockage of coronary arteries and as a result prevent the heart from receiving blood, oxygen, and vital nutrients. Plaque causes blockage by two mechanisms: 1) progressive narrowing of the artery due to the plaque compromising the vessel lumen, and 2) thrombotic occlusion of the artery, which occurs when the hard surface of a plaque tears or breaks off, exposing the inner fatty pro-thrombotic, platelet-attracting components to the site, resulting in enlargement of the blockage. The resulting reduction in blood flow can be either acute or chronic and leads to an imbalance in the blood supply to the myocardium and thus increases the requirements of the myocardium for oxygenated blood either at rest or during exertion.^{5,6} Areas of atherosclerosis can also cause vascular dysfunction, which is an imbalance between relaxation and constriction in either large conduit arteries or the microcirculation. This process can occur in areas of plaque development or can occur in the absence of significant plaque but in the presence of certain predisposing diseases or atherosclerotic risk factors (e.g., lipid disorders, diabetes, smoking, and sedentary lifestyle).

The most common symptom of obstructive CAD is chest pain, which is the first presenting symptom in up to at least 50 percent of patients with CAD.⁷ Other common symptoms include dyspnea or early fatigue with exertion, indigestion, palpitations, tightness in the throat, and neck or arm pain. When documented to be associated with CAD, these symptoms are referred to as “anginal equivalents.” However, because these symptoms are also seen in many common noncardiac conditions such as gastroesophageal reflux, esophageal spasm, and cervical disc disease, they are much less reliable predictors of CAD. Women and people with diabetes are less likely to experience classic angina, adding to the challenges of early CAD diagnosis in these populations. Although the onset of symptoms and clinical impact of CAD depend in part on the number and distribution of atheromatous plaques, the degree and length of coronary narrowing, microvascular function, and cardiac blood flow demand (determined by factors such as degree of usual daily activity, blood pressure and heart rate), lesion severity is poorly correlated with symptoms and CAD may remain asymptomatic for many years.

Patient Assessment and Pretest Risk of CAD

The 2012 ACCF/AHA Guideline categorizes the pretest probability of CAD as low (<10%), intermediate (10%–90%) or high (>90%).⁸ Estimation of pretest probability starts with evaluation of patient history and presentation, including type of chest pain, age, and sex. Pretest risk of CAD can be based on a number of factors, including the presence of risk factors such as diabetes mellitus, hypertension, dyslipidemia, personal smoking history, and family history of premature atherosclerotic cardiovascular disease; however, pretest risk is often ascertained based on age, sex and type of chest pain (i.e., typical or atypical).⁹ Chest pain has classically been subdivided into typical (or definite) angina, atypical (or probable) angina, and nonanginal chest pain. Typical cardiac angina is characterized by (1) a substernal discomfort which is precipitated by physical exertion or emotional stress, (2) is relieved by rest or nitroglycerine in less than 10 minutes, and (3) may be accompanied by radiation of the discomfort to either shoulder, to the jaw, or to the inner aspect of the arm. Atypical angina is that which meets only two of the three characteristics of typical angina, while nonanginal chest pain only meets only one of the three characteristics of typical angina. The type of chest pain together with age and sex allow for a rough estimation of pretest probability of CAD using validated clinical risk scores such as the Diamond and Forrester Chest Pain Prediction Rule.^{10, 11} Using this algorithm, a 55-year-old man presenting with typical chest pain would be estimated to have approximately 80 percent probability of having obstructive CAD; but this pretest likelihood would be 50 percent if the pain were atypical and 33 percent if it was nonanginal in nature. There are a number of other clinical risk prediction tools for bedside prediction of pretest probability in patients with suspected CAD, including the Morise Score, TIMI (Thrombolysis in Myocardial Infarction) risk score, and the Goldman Reilly criteria (Goldstein).^{12, 13, 14-16} However, these are rarely documented in clinical practice and baseline level of risk often revolves around the clinician's overall assessment of sociodemographic characteristics, the description of the chest pain, and the findings on resting ECG.¹⁷

Diagnosis of CAD: Overview

The first step in diagnosing CAD is a thorough clinical work-up which consists of a physical examination, patient history, obtaining some combination of a resting ECG, chest x-ray, and/or serum biomarkers such as cardiac troponins. If the cardiac troponins are consistent with myocardial injury or the ECG is suggestive of myocardial ischemia then patients should be treated according to the appropriate guidelines for an acute coronary syndrome (ACS).¹⁸

If the presentation is not acute, the ECG is nonspecific, and cardiac troponins are normal, then the stable patient may be discharged. Alternatively, the patient may receive further testing to help determine the etiology of chest pain and the appropriate management, in which case the risk of CAD must be assessed based on patient history and presentation. A patient's pretest CAD risk can inform which test or procedure are most appropriate as a first step towards diagnosing CAD.

A diagnosis of CAD can be made by looking for evidence of the pathophysiologic processes of disease, including anatomic changes of the arterial wall, impaired myocardial perfusion, or consequences of impaired perfusion such as myocardial contractile dysfunction. Historically, invasive coronary angiography (ICA) has been considered the standard reference diagnostic test for anatomic CAD (defined here as any obstructive lesion that is consistent with symptoms or which may carry an increased risk of ACS); although its invasive nature makes it less ideal in many patients due to its associated risks and costs. Noninvasive tests are another option, and

provide diagnostic and prognostic information that can improve risk stratification and thus guide subsequent testing and interventions. Noninvasive diagnostic tests can be broadly divided into two categories: functional tests and anatomic tests. Functional tests provide additional information not provided by standard ICA, such as whether symptoms are correlated with areas of ischemia. Functional tests include exercise electrocardiography (ECG), exercise/pharmacologic stress echocardiography, exercise/pharmacologic cardiac nuclear imaging with single photon emission computed tomography (SPECT) or positron emission tomography (PET), pharmacologic stress magnetic resonance imaging (MRI), computed tomography (CT), and Doppler ultrasound-derived flow reserve measurements. Noninvasive anatomic tests include coronary CT angiography (CCTA) and coronary artery calcium scoring (CACs). American College of Cardiology Foundation/American Heart Association (ACCF/AHA) appropriate use criteria suggest that, as a general rule, functional testing is more informative than noninvasive anatomic evaluation and exercise testing is more informative than pharmacologic testing.¹⁹ Each of these tests is described in more detail in the following sections.

Impact of Pretest Risk on Choice of Diagnostic Test

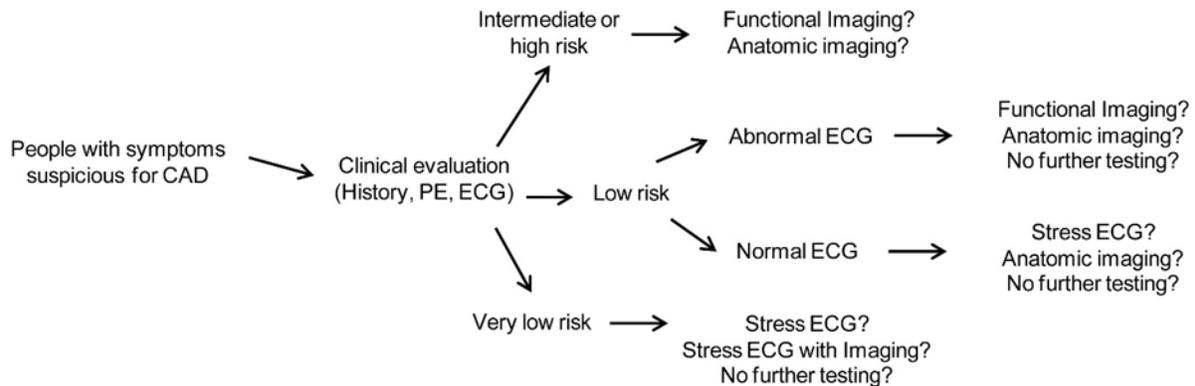
Further diagnostic testing beyond the resting ECG may be considered appropriate in patients who are symptomatic based on whether they are considered as low (less than 10% pretest probability of CAD), intermediate (10%–90% pretest probability of CAD), or high (greater than 90% pretest probability of CAD). The 2012 ACCF/AHA guideline states that diagnostic testing is most valuable when the pretest probability of ischemic heart diseases is intermediate (10%–90%) and provides a range of options for which test may be used in a given scenario. However, the effectiveness of different modalities with regard to impact on clinical outcomes are not compared.⁸ Currently, clinical practice utilizes a variety of tests as the initial (and additional) diagnostic tests for patients at intermediate pretest risk of CAD.

Three primary areas of uncertainty exist regarding which tests, if any, may be most suitable and most beneficial for specific patient scenarios in patients who present with symptoms suggestive of CAD but have no prior history of it, and these areas helped to frame to Key Questions of this systematic review. Namely:

- In patients with low pretest probability of CAD (<10%), are clinical outcomes improved by use of nonimaging stress testing, imaging stress testing, or no further testing? It is not clear whether imaging may be necessary in this group of patients or if there are specific subgroups of low risk patients who might benefit more from one type of testing or who should have no further testing.
- How do tests compare with regard to improvement in clinical outcomes in very low (<5%) or low risk patients? How do tests compare in intermediate to high risk patients? Important clinical outcomes include prevention of myocardial infarction (MI), premature mortality, and congestive heart failure. How do test differ in their ability to reclassify patient risk after the test and influence appropriate patient management?
- Are there differences in clinical outcomes following anatomic versus functional testing in either of the above risk groups?

The overarching conceptual flow for initiating noninvasive testing based on pretest risk assessment is shown in Figure 1.

Figure 1. Overarching conceptual flow for initiating noninvasive testing based on risk assessment following initial clinical evaluation



CAD = coronary artery disease; ECG = electrocardiogram; PE = physical exam.

Patients at low pretest risk may undergo noninvasive testing to further delineate their risk and to provide a basis for clinical decisionmaking, though in some cases, an alternate explanation for the symptoms (such as heart burn, costochondritis, or pulmonary disease) may be evaluated first. Patients at intermediate risk commonly undergo noninvasive testing followed by appropriate treatment for comorbidities and risk factors. The ACCF/AHA intermediate range is intentionally broad reflecting the availability of noninvasive tests that have been viewed as both safe and effective to further stratify risk in the “intermediate pretest risk” category. In other words, the low end of the intermediate range is extended irrespective of cost because of the important health consequences of missing disease, but also results in a situation where testing is performed in a very large number of individuals who do not have disease.⁹ The high end is extended because of the combination of the somewhat high cost and risk of ICA and reasonably high sensitivity of testing to detect high risk obstructive disease. Patients at high risk may undergo noninvasive testing, although at times clinicians may appropriately decide to bypass noninvasive stress testing and proceed directly to ICA.¹⁹ This is more frequently done in patients who present to the emergency room with typical symptoms. In patients where clinical judgment remains equivocal, an additional test to further identify risk may be pursued.

Noninvasive Diagnostic Tests

Noninvasive Functional Tests

Functional tests of interest include exercise electrocardiography (ECG), exercise/pharmacologic stress echocardiography, exercise/pharmacologic cardiac nuclear imaging with single photon emission computed tomography (SPECT) or positron emission tomography (PET), and pharmacologic stress magnetic resonance imaging (MRI). Additional details for each test are available in Table 1.

Exercise ECG is often the recommended initial test. Exercise testing is more physiologic and allows for documentation of the workload at which a patient develops symptoms or ischemia (defined as >1 mm ST depression in 2 contiguous ECG leads). Exertional capacity (measured in metabolic equivalents) and hemodynamic response (abnormal heart rate or blood pressure response) to exercise also provides important prognostic information.²⁰ The Duke treadmill score

incorporates the exercise time, development of symptoms, and ST segment deviation a treadmill test and has been correlated with outcomes.²¹ Exercise testing is widely available, does not require intravenous access or radiation exposure is relatively inexpensive, and is widely validated. Despite these advantages, there are limitations including the fact that some patients are unable to exercise, some may have certain baseline ECG abnormalities that make the ECG uninterpretable during stress (left bundle branch block, left ventricular hypertrophy with repolarization abnormalities, ST segment depression of greater than or equal to 1 mm, and ventricular pre-excitation), and certain medications can cause false positive ST changes (notably digoxin).²⁰

Stress echocardiography may be performed with exercise or through pharmacologic means (typically dobutamine). Stress echocardiography boasts improved sensitivity and specificity compared to ECG with improved localization of the at risk territory in a similar examination time frame and without radiation. It is limited by a poor image quality (often due to body habitus or pulmonary disease) and is operator dependent with a semi-quantitative evaluation.

SPECT and PET are two forms of radionuclide imaging. Of the two, SPECT is more readily available and more commonly used. PET testing is much less frequently used due to limited availability and a relatively high cost. SPECT can be performed with exercise or pharmacologic agents and offers improved sensitivity and specificity compared to ECG testing and comparable diagnostic characteristics compared to echocardiography.^{22, 23} In the case of patients with poor echocardiographic quality or left bundle branch block, this is the preferred test. SPECT can also be limited by artifacts from breast tissue, motion, and liver/gallbladder uptake of the imaging agents. While SPECT relies on relative blood flow and can miss balanced ischemia, PET provides absolute quantification of blood flow and offers improved visual certainty which translates into improved sensitivity and specificity.²⁴ Radionuclide imaging requires exposure to radiation which ECG testing and echocardiography do not.

Cardiac magnetic resonance imaging is an imaging modality which offers the ability to evaluate rest and stress perfusion for ischemia, cine imaging for cardiac function, and late gadolinium enhancement for evaluation of prior infarction. The operational diagnostic characteristics are superior to echocardiography and SPECT imaging.^{25, 26} Despite its improved sensitivity and specificity, this modality is not readily available in part due to high cost and limited availability. An additional concern is the uncertainty regarding possible increased downstream testing and unintended findings.²⁷ Due to technological limitations it is also, practically, limited to pharmacologic stress agents.

Noninvasive Anatomic Tests

Noninvasive anatomic tests include CCTA and CACS, although CACS is rarely considered appropriate in symptomatic patients. Additional details for each test are available in Table 2.

CCTA is a relatively accessible test that has a rapid scanning time. The necessary hardware is available in most hospitals, and state of the art machines have a 64-slice scanner and the ability to inject contrast. Software packages available for most modern CT scanners assist in the acquisition and processing of images. However, there are many patient related factors which can interfere with diagnostic quality including irregular heart rate (such as atrial fibrillation), heart rates that are too fast (>70 bpm), inability to sustain a breath hold for five seconds, severe calcification of the coronary arteries, and small coronary artery vessel diameter (< 1.5 mm). There are additional risks incurred by the injection of iodinated contrast agents for patients who have a history of allergy or those with reduced renal function and there is some radiation exposure. Overall, adoption of CCTA has been low in clinical practice, being favored for

patients considered at low risk for CAD due to its perceived high negative predictive value. It is often perceived as a “rule-out” test for CAD.²⁸⁻³¹

CACS is obtained through performance of a noncontrast computed tomography scan followed by a post-processing algorithm to determine an Agatston score, a volume score, or the presence of a calcium mass. The most widely used and best established measure of coronary artery calcium is the Agatston score. CACS is readily obtained and highly reproducible, and is most frequently used in asymptomatic patients for cardiovascular risk assessment. CACS is rarely appropriate for symptomatic patients, as the inability to detect calcium in the coronary arteries does not eliminate the possibility of significant stenoses.^{19, 32}

Table 1. Overview of included functional noninvasive tests

Test	General Use	Advantages	Disadvantages	Diagnostic Threshold and Posttest Risk
<p>Exercise Electrocardiography, Exercise Treadmill Testing</p>	<ul style="list-style-type: none"> • Preferred initial test if there are no contraindications • Not appropriate if there are baseline abnormalities in the ECG • Not appropriate for patients who cannot exercise (leg claudication, deconditioning, arthritis, pulmonary disease) • Typically avoided in premenopausal women due to poor sensitivity and specificity • Typically performed on a treadmill using various protocols (commonly Bruce protocol) 	<ul style="list-style-type: none"> • Low cost; quick • Functional capacity assessed • High sensitivity for prognostic 3-vessel disease or left main CAD 	<ul style="list-style-type: none"> • Suboptimal sensitivity • Low detection rate for single vessel disease • Nondiagnostic with abnormal ECG • Patient needs to achieve maximum heart rate • Wide variability in sensitivity and specificity for exercise ETT has been reported across studies • There are specific ECG criteria which determine positive and high-risk for a treadmill test 	<p>Abnormal:</p> <ul style="list-style-type: none"> • >1 mm ST depression in 2 contiguous leads • Arrhythmia • Below average exercise capacity <p>High risk:</p> <ul style="list-style-type: none"> • Stress Score less than or equal to -11 • Abnormal hemodynamic response
<p>Stress Echocardiography (exercise or pharmacologic)</p>	<ul style="list-style-type: none"> • Assessment of ventricular size and function • Assessment of wall motion abnormalities • Visual assessment of myocardial response to stress agent. • Exercise can be upright or supine bicycle or treadmill • Dobutamine can be used for patients unable to exercise • Preferred in those who are unable to exercise • Can be used in patients with abnormal ECGs (except LBBB) 	<ul style="list-style-type: none"> • Improved sensitivity & specificity compared to ECG • Short exam time; simple and convenient to perform • No radiation • Evaluate cardiac function and structural abnormalities at the same time • Allows localization of ischemia • Exercise and dobutamine stress have similar value 	<ul style="list-style-type: none"> • Decreased sensitivity for detection of single vessel disease or mild stenosis with post-exercise imaging • Infarct zone ischemia can be difficult to detect • Operator dependent; no quantitative analysis • Limited by poor image quality (body habitus, pulmonary disease) and interpretation is more difficult if resting wall motion abnormalities 	<p>Abnormal:</p> <ul style="list-style-type: none"> • New WMAs with stress • Abnormal LVEF with stress <p>High Risk:</p> <ul style="list-style-type: none"> • LVEF <35% at rest or during exercise • WMA involving at least 2 of 16 segments developing with exercise or low dose dobutamine (10 mcg/kg/min) on a stress echocardiography • WMA (>2 segments) developing at a low heart rate (<120 bpm) • Evidence of extensive ischemia on stress testing

Test	General Use	Advantages	Disadvantages	Diagnostic Threshold and Posttest Risk
<p>Single Photon Emission Computed Tomography, aka myocardial scintigraphy, aka nuclear stress testing (this may be combined with scintigraphy or planar imaging)</p>	<ul style="list-style-type: none"> Assessment of ventricular size and function (computer generated) Assessment of wall motion abnormalities (visual assessment; quite limited) Assessment of viability Preferred for patients with LBBB Appropriate for those with poor echocardiography windows Stress agents include : regadenoson, adenosine, dipyridamole, & dobutamine Imaging agents include: 99mTc-MIBI (sestamibi), thallium, technetium, & tetrofosmin 	<ul style="list-style-type: none"> Evaluate perfusion (both viability and ischemia) and function Improved sensitivity & specificity compared to ECG Exercise and pharmacologic stress have similar value Can be quantitative 	<ul style="list-style-type: none"> Limited by soft tissue attenuation (body habitus, breast artifact, & liver artifact) & motion artifact. Involves radiation exposure (~12 mSv to 37 mSv if dual isotope protocol used) Relative flow not absolute (can miss 3 vessel disease due to “balanced ischemia”) 	<p>Abnormal:</p> <ul style="list-style-type: none"> Any perfusion defect WMAs <p>High Risk:</p> <ul style="list-style-type: none"> Perfusion defect representing ≥10% of myocardium (particularly if anterior) Multiple moderate perfusion defects Large fixed defect with transient ischemic LV dilation or increase in Lung to Heart Ratio Stress induced moderate defect with transient ischemic LV dilation or increase in Lung to Heart Ratio
<p>Stress Positron Emission Testing</p>	<ul style="list-style-type: none"> Rarely used clinically Preferred in women and obese patients Assessment of ventricular size and function (visual with computer aid) Assessment of ischemia & viability 	<ul style="list-style-type: none"> Accurate quantification of blood flow (absolute) due to trace kinetic modeling and attenuation correction PET has higher interpretive certainty than SPECT due to improved image quality (in particular for women and obese patients) Measures absolute myocardial blood flow 	<ul style="list-style-type: none"> Restricted to pharmacologic stress High cost Low availability Radiation exposure (10–14 mSv) Data to support PET is limited 	<p>Abnormal:</p> <ul style="list-style-type: none"> Any perfusion defect <p>High Risk:</p> <ul style="list-style-type: none"> Perfusion defect representing ≥10% of myocardium (particularly if anterior)

Test	General Use	Advantages	Disadvantages	Diagnostic Threshold and Posttest Risk
<i>Stress Cardiac Magnetic Resonance Imaging</i>	<ul style="list-style-type: none"> • Rarely used clinically • Typically receive assessment of structure and function at the same time and can assess some cardiac indices (stroke volume) • Typically pharmacological 	<ul style="list-style-type: none"> • High spacial resolution • Imaging of arterial wall and plaque • Flow mapping with contrast • Visualization of subendocardial perfusion • Assessment of viability (delayed gadolinium enhancement, does not require stress agents) • No radiation • Can provide anatomical evaluation as well 	<ul style="list-style-type: none"> • Costly • Long procedure time • Not readily available 	<p>Abnormal:</p> <ul style="list-style-type: none"> • Any perfusion defect • Wall motion abnormality <p>High Risk:</p> <ul style="list-style-type: none"> • >3 of 32 stress perfusion defects • >2 dobutamine-induced dysfunctional segments (out of 17 segments)

CAD = coronary artery disease; ECG = electrocardiography; ETT = exercise treadmill test; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; mSv = milliSeivert; PET = positron emission tomography; SPECT = single photon emission computed tomography; WMA = wall motion abnormality.

Table 2. Overview of included anatomic noninvasive tests

Test	Use	Advantages	Disadvantages	Diagnostic Threshold and Posttest Risk
<p>Coronary Computed Tomography Angiography (≥64 slice)</p>	<ul style="list-style-type: none"> • Used as a rule-out test for low likelihood patients with chest pain • Identify or exclude coronary luminal diameter stenoses exceeding 50%. • Clinically used in patients (assuming no diagnosis of CAD) with atypical symptoms or nondiagnostic results of a stress test or those at high risk for catheterization • In practice it is most common to use 64-slice or more • Can be retrospective or prospective (ECG-gated) • In EBCT or MDCT the X-ray source point is stationary, but electron beam is swept electronically • This will almost always include a coronary artery calcium score • Contrast agents used include: iopamidol (Isovue), iohexol (Omnipaque), ioversol (Optiray), ioxilan (Oxilan), ioxaglate (Hexabrix), and iodixanol (Visipaque) 	<ul style="list-style-type: none"> • Noninvasive angiogram to rule out significant stenosis • Unlike cardiac CT-quantified calcium scoring, angiography detects obstructive CAD • Rapid • Good negative predictive value • Other causes of chest pain (aortic aneurysm) • High sensitivity 	<ul style="list-style-type: none"> • Ischemia not confirmed • Quality depends on slow heart rate • Specificity 60-80% • Distal vessels difficult • Cardiac motion artifact • Poor quality if heart rate not well controlled (requires beta blockers) • Heavy calcification causes “bloom artifact” limiting assessment of lumen • Fractional flow reserve is limited to proprietary software with limited validation (excluded from this analysis) • Required reconstruction of images and is time intensive • Radiation exposure (modern is ~3 mSv) • Limited by fast or irregular heart rate and/or motion 	<p>Abnormal:</p> <ul style="list-style-type: none"> • Any luminal irregularities <p>High Risk:</p> <ul style="list-style-type: none"> • Left main ≥50% narrowing • Proximal LAD ≥70% narrowing • 3 vessel disease • Left main equivalent (i.e. proximal LAD and proximal circumflex artery)

Test	Use	Advantages	Disadvantages	Diagnostic Threshold and Posttest Risk
Coronary Artery Calcium Score	<ul style="list-style-type: none"> • Typically used as a screening test for asymptomatic patients • Uses the amount of calcium present in an artery to calculate a score (typically using Agatston method) • Can be performed using most CT modality and does not require contrast agent 	<ul style="list-style-type: none"> • Screening test for asymptomatic patients to detect coronary artery calcium 	<ul style="list-style-type: none"> • Does not detect ischemia or degree of vessel narrowing • Radiation exposure 	<p>Various thresholds exist. The presence of any calcium in a young population is abnormal (i.e. score >0) and any calcium is associated with a higher risk. There are age/sex matched norms. >100 is associated with a 10 fold higher risk than zero. >400 is considered an indication for statin in the current guidelines regardless of other risk factors.</p>

CAD = coronary artery disease; EBCT = electron beam computed tomography; MDCT = multidetector computed tomography; LAD = left anterior descending artery.

Invasive Coronary Angiography

Historically, ICA has been considered the standard reference diagnostic test for anatomic CAD and provides information on coronary artery anatomy and lumen obstruction through introduction of a radiopaque contrast dye while obtaining concurrent fluoroscopic cine images. ICA allows visualization of the size, position, and possible stenotic areas in vessels. Various thresholds for occlusion have been used (e.g., $\geq 50\%$ or $\geq 70\%$ occlusion) for diagnosis of CAD. Access to the arterial system is most commonly obtained through placement of a sheath in the femoral or the radial artery and requires instrumentation in the ascending thoracic aorta proximal to the head vessels. Complications and death are rare in ICA procedures with a majority of the literature reporting ICA harms being case studies. Adverse reactions to the contrast dye may occur, including allergic response; renal dysfunction; vascular injury including arterial dissection or perforation; and embolism including strokes, transient ischemic attacks, or limb ischemia. In addition, the procedure exposes patients to ionizing radiation.

ICA may overestimate or underestimate disease depending on a variety of technical factors as well as the complexity of coronary anatomy and plaque configuration. Many lesions are eccentric, so the apparent degree of stenosis can vary depending on the angle of visualization, and reproducibility on measurement of stenosis is considered only moderate.^{8, 33-35} ICA depicts coronary anatomy in a planar two-dimensional silhouette of the arterial lumen and interpretation can be confounded by vessel tortuosity, overlap of radiodense structures, and irregularities in plaque shape or flow of the contrast dye.³⁴ There are aspects of the coronary anatomy which portend a high risk for future events including arterial remodeling, and many high risk features of a plaque (e.g., a vulnerable plaque) are not evident with ICA. ICA serves best as reference standard for anatomic tests and to date, there is not a comparable reference standard for tests evaluating functional changes secondary to ischemic heart disease. These limitations have led some to question the true value of ICA as the best reference standard for determining test accuracy, particularly for functional tests. Efforts to improve the diagnostic accuracy of coronary angiography have led to intravascular ultrasound (IVUS) and fractional flow reserve (FFR) though both techniques are reliant on having obtained earlier angiographic views.

Accuracy of Noninvasive Test Compared With ICA

Increasingly, experts in cardiovascular health indicate that evidence on the value of noninvasive diagnostic cardiovascular testing needs to expand beyond traditional measures of test performance, such as sensitivity and specificity compared with a given reference standard and focus on evaluating the impact of such testing on hard cardiovascular outcomes.³⁶ Thus, while diagnostic accuracy measures provide important information on test performance, the primary focus of this report is to determine whether noninvasive tests improve clinical health outcomes and impact patient management. In keeping with this focus, information on the traditional test parameters of diagnostic accuracy are described here in order to provide a foundation for the report and were not examined via the formal systematic review process.

To provide a general overview of the diagnostic accuracy of the included noninvasive tests in the target population of symptomatic patients without known CAD, a targeted search of the literature was done to identify one or two moderate- to high-quality systematic reviews (based on the AMSTAR checklist³⁷) that compared noninvasive tests included in this report (see Tables 1 and 2 above) with the historic gold standard of ICA in terms of traditional diagnostic test

performance measures (i.e., sensitivity, specificity, positive/negative predictive value, positive/negative likelihood ratio).

The diagnostic test characteristics of all the included tests compared with the test results from ICA are summarized in Table 3, with more specific details available in Appendix H. The values of the various diagnostic test characteristics in these tables were taken from or calculated from the values reported in the included systematic reviews. Measures of diagnostic accuracy among patients with suspected CAD varied among the various tests: sensitivity ranged from 62 percent to 100 percent; specificity ranged from 68 percent to 89 percent; positive predictive value ranged from 57 percent to 94 percent; and negative predictive value ranged from 72 percent to 99 percent. Exercise electrocardiography (ECG) had the lowest overall diagnostic accuracy; and CCTA had the highest diagnostic accuracy relative to ICA, which is perhaps consistent with CCTA as the test most similar to ICA in what it measures. The two tests classified as anatomic tests (CACS and CCTA) had the highest negative predictive values, which indicate a lower percentage of patients with significant coronary artery stenosis by ICA that would be missed by these two tests. Otherwise, there is no clear pattern to the test characteristics of the different tests. For individual tests or across various tests, there is also no clear pattern in the differences between test characteristics among patients suspected of CAD only compared with all patients (i.e., suspected CAD and known CAD combined). The fact that the functional tests had lower negative predictive values does not imply that these tests would necessarily perform worse than ICA for purposes of predicting clinical outcomes such as worsening angina, incident MI or CAD death, which is the focus of the current systematic review.

Table 3. Summary of diagnostic accuracy of noninvasive tests compared with invasive coronary angiography

Test	Population	Sensitivity	Specificity	PPV	NPV	LR +	LR -	Prevalence
Exercise Electrocardiography	Overall*	67%	46%	41%	72%	NR	NR	NR
	Suspected CAD	62%	68%	57%	72%	1.94	0.56	41%
Stress Echocardiography	Overall†	84–87%	72–77%	85–89%	69–73%	3.08–3.65	0.18–0.21	66–68%
	Suspected CAD	88%	89%	93%	80%	8.35	0.13	64%
Single Photon Emission Computed Tomography	Overall	83–85%	77–85%	79–85%	79–85%	3.56–5.13	0.18–0.22	50%
	Suspected CAD	83–84%	79–85%	72–85%	84%	3.88–5.01	0.19–0.21	41%‡
Positron Emission Tomography	Overall	82–90%	86–88%	93–96%	53–84%	5.57–5.88	0.11–0.21	63–80%
	Suspected CAD	90–91%	82–91%	94%	75–84%	4.97–8.89	0.11	75%‡
Stress Magnetic Resonance Imaging	Overall	83%	86%	94%	68%	5.93	0.20	71%
	Suspected CAD	81%	87%	93%	70%	6.39	0.21	67%
Coronary Artery Calcium Scoring	Suspected CAD	98–99%	35–40%	65–68%	93–95%	1.51	0.04	55–56%
Coronary Computed Tomography Angiography	Suspected CAD	100%	89%	93%	99%	9.2	0.00	58%

CAD = coronary artery disease; LR + = positive likelihood ratio; LR - = negative likelihood ratio; angiography; NPV = negative predictive value; NR = not reported; PPV = positive predictive value.

*Values for diagnostic test measures are taken from or derived from systematic reviews cited in Appendix H

†Values reported are for combined groups of patients with known CAD and patients with suspected (but not confirmed) CAD.

‡Mean prevalence only available or calculable for one of the two included reviews.

Radiation Exposure in Noninvasive Cardiac Testing

Medical imaging is the largest controllable source of radiation exposure to the American public³⁸ and scrutiny of cardiac imaging procedures has increased based on concerns related to greater utilization and lack of adherence to quality control procedures.³⁹ In clinical decisionmaking, the levels of exposure for a given test need to be put in the context of other radiation-utilizing tests that may be part of the clinical pathway, as the possible cumulative effects of repeated radiation exposure are of concern. Potential benefits and risks, including any related to not performing the test, should be carefully considered before ordering tests that will expose patients to ionizing radiation. Final determination of net benefit for a given clinical scenario reflects the values and judgments of the individuals making the decisions.

Current guidance from regulatory bodies is that no threshold exists and that exposure should be kept as low as reasonably achievable (ALARA). ALARA takes into consideration the importance of assessing the “benefit to risk ratio” to balance the importance of information needed from a procedure with the potential risks related to radiation exposure.

ACCF/AHA clinical guidelines recommend following ALARA in all patient populations and provide recommendations for specific cardiac testing modalities that involves ionizing radiation and note that care should be taken when exposing low risk patients, particularly young patients, to ionizing radiation.⁸ They further note that all noninvasive stress testing carries some risk, even if ionizing radiation is not involved. The American College of Radiology reports that ICA is not usually appropriate for diagnosing coronary artery disease in patients with low probability.⁴⁰ SPECT, CCTA, echocardiography, and MRI are all considered more appropriate than ICA for low CAD probability. Of these modalities, the ACR considers CTA with various contrast and dose techniques to be the most appropriate – receiving the rating of “usually appropriate”.

To date, no large-scale epidemiologic studies evaluating cancer risk associated with cardiac imaging procedures involving ionizing radiation have been published, and there is uncertainty and controversy with regard to the actual risk of low dose radiation from cardiac testing. For context, estimates of typical effective dose for environmental and medical sources of radiation are outlined in Table 4. Some radiation exposure occurs naturally and during activities of daily living. As seen below, estimated radiation dose for various noninvasive tests for CAD vary by test. The effective doses for imaging techniques from studies included in this report range from <1 mSv to 16 mSv. The values in the following table are based on literature estimates and are subject to change dependent on the imaging parameters utilized.

Table 4. Overview of radiation exposure ranges*

Radiation Exposure Type		Total Effective Dose (mSv)	
Environmental Exposures	Round-trip flight, New York – Seattle	0.06	
	Naturally occurring	3/year	
	July 1971 lunar landing	5	
	Nuclear worker	20	
	Atomic bomb survivor	200	
Diagnostic and Procedural Exposures	ECHO	0	
	CMRI	0	
	ECG	0	
	Dental CT	0.2	
	Mammogram	0.4	
	CACS	Range found in studies in this report	0.69–0.8
		Range reported in Einstein 2014	1–5
	ICA	Range reported by Einstein 2014	2–20
		Range reported by ACR	1–10 (with or without ventriculography)
	CCTA	Range found in studies in this report	3.8–15.1
		Range reported in Einstein 2014	<0.5–50
		Range reported by ACR	1–30 (using various contrast and dose techniques)
		Range reported by Cerqueira 2010	5–10
	Fluoroscopy for PCI	Range reported by Einstein 2014	5–57
	PET	Range found in studies in this report	6.0
		Range reported in Einstein 2014	7 (FDG)
	SPECT	Range found in studies in this report	10.5–14
		Ranges reported in Einstein 2014	2.3–14 (^{99m} Tc Tetrofosmin); 2.7–18 (^{99m} Tc Sestamibi); 15 (²⁰¹ Tl); 22 (²⁰¹ Tl/ ^{99m} Tc Tetrofosmin dual-isotope); 23 (²⁰¹ Tl/ ^{99m} Tc Sestamibi dual-isotope)
		Range reported by ACR	10–30
		Reported by Halliburton 2011	11 (^{99m} Tc)
	Coronary radiofrequency ablation		15
	Pelvic vein embolization		60

CACS: coronary artery calcium scoring, CCTA: coronary computed tomography angiography, CMR: cardiac magnetic resonance imaging, ECG: electrocardiogram, ECHO: echocardiography, ICA: invasive coronary angiography, mSv = milliSeiverts; PCI: percutaneous coronary intervention; PET: positron emission tomography, SPECT: single photon emission tomography.

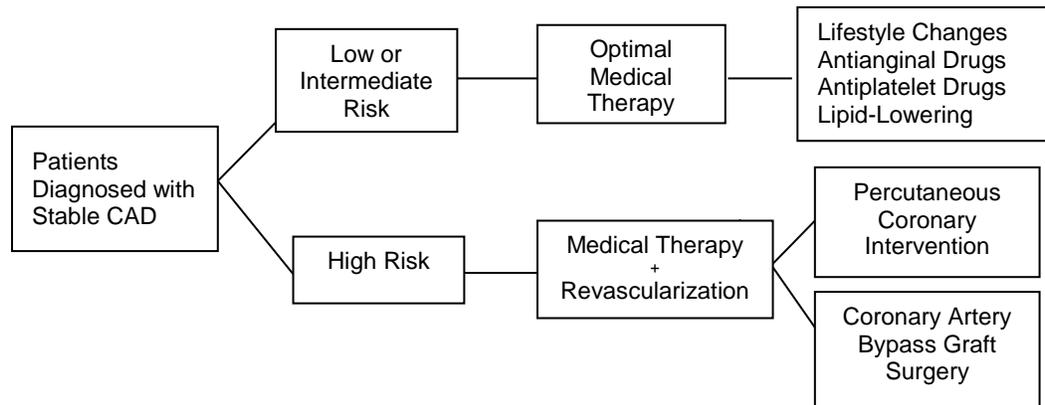
*Adapted using data from³⁸⁻⁴³

Treatment of Stable CAD

The goal of testing is to identify people who would benefit from treatment. Where efficacious treatment is available and test costs and adverse events are comparable, test sensitivity may be most important to consider. In situations where there is little difference in treatment outcomes, avoiding false positives is important and thus specificity may be more important. The focus of this report is on stable, symptomatic patients without prior CAD presenting for an initial test to determine the presence of CAD. There are a number of treatment options for this population. The extent to which a tests leads to the appropriate treatment is reflected in the impact on clinical outcomes. Because one of the outcomes of interest for this report is whether noninvasive tests differ in terms of referral for treatment (e.g., revascularization), a brief background on treatment options is provided here.

Treatment of stable CAD is initially guided by the patient’s posttest risk stratification, symptoms, and non-CAD comorbidities.^{8, 44, 45} Based on the predicted annual cardiac mortality rate, recent clinical guidelines provide thresholds of low risk ($\leq 1\%$ per year), intermediate risk (1% to 3% per year), and high risk ($\geq 3\%$ per year).⁸ As shown in Figure 2, patients considered to be at low or intermediate risk of cardiac mortality should generally be treated with medical therapy alone, while those found to be at high risk should receive both medical therapy and revascularization.

Figure 2. Initial treatment pathways for patients diagnosed with CAD



CAD = coronary artery disease.

Medical Therapy

Optimal (or guideline-directed) medical therapy is optimized on a per-patient basis depending on patient characteristics and guideline recommendations. Medical therapy includes lifestyle modifications (physical activity, smoking cessations, weight management, and dietary changes), treatment of secondary conditions such as diabetes and hypertension, risk modification with antiplatelet drugs, management of lipid levels, and treatment of angina symptoms if present.

Lifestyle interventions, including primary risk reduction strategies such as exercise and increased physical activity, smoking cessation, and weight management are associated with lower rates of cardiovascular outcomes, and can improve outcome following a nonfatal event. Both antiplatelet drugs (primarily aspirin) and lipid-lowering drugs (e.g., statins) are used to reduce the risk of thrombotic coronary events through stabilization of the coronary plaque to

prevent rupture and thrombosis. Angina is treated with a variety of drugs that reduce myocardial oxygen demand and therefore reduce anginal events, including beta-blockers, calcium channel blockers, nitrates and ranolazine. Beta-blockers are typically recommended as first line due to evidence that they reduce the risk of mortality post-MI and in those with hypertension. In low to intermediate risk patients treated only with medical therapy, the benefits of initial treatments identified in Figure 2 are outlined in Table 5, below.

Table 5. Effects of medical therapy for stable coronary artery disease

Intervention	Purpose of Treatment	Coronary Event Benefits	Potential Harms
Antiplatelet; Aspirin	Reduce risk of clot development	33% reduction in serious vascular event such as nonfatal MI, nonfatal stroke, or vascular death. ⁴⁶	Risk of a major extracranial bleed with aspirin (<75 to 325 mg): odds ratios 1.4 to 1.7; absolute event rates 1.8 to 2.5%. ⁴⁶
Lipid-lowering; Statins	Reduce risk of cholesterol-related effects	18% reduction in coronary death rate, 24% reduction in the composite of nonfatal MI or coronary death, nonfatal or fatal stroke and coronary or noncoronary revascularization. ⁴⁷ 22% reduction in risk of CAD death, nonfatal MI, resuscitation after cardiac arrest, or fatal or nonfatal stroke with high dose versus standard dose statin (i.e. atorvastatin 10 mg versus 80 mg). ⁴⁸	Potential myalgias, rhabdomyolysis, elevated liver enzymes.
Beta-blockers	Reduce angina symptoms	At least 50% reduction in the frequency of angina attacks. ⁴⁹ No impact on cardiovascular outcomes except when used post-MI.	Potential reduced heart rate with exercise, low blood pressure, lethargy
Calcium channel blockers	Reduce angina symptoms	Both dihydropyridines and nondihydropyridine calcium channel blockers reduce the frequency of angina attacks by at least 50%. ⁵⁰ Benefit on cardiovascular outcomes has not been shown.	Peripheral edema, flushing, headaches Verapamil: constipation short-acting nifedipine: reflex tachycardia. Verapamil and diltiazem: reduce cardiac contractility and slow cardiac conduction.
Nitrates	Reduce angina symptoms	Immediate release preparations used for treatment of acute angina. Longer acting forms improve exercise tolerance and reduce degree of ST segment depression during exercise, but tolerance develops quickly. Intermittent dosing may help. No benefit in the frequency of angina attacks has been found. ⁵¹	Flushing, headache hypotension. Development of tolerance. Multiple contraindications exist.
Ranolazine	Reduce angina symptoms	22% reduction in recurrent ischemia, 33% reduction in worsening angina, results in greater exercise duration (514 versus 482 seconds). ⁵²	Dose-dependent increase in the QT interval; multiple contraindications and drug interactions exist.

CAD = coronary artery disease; MI = myocardial infarction.

Revascularization

Revascularization methods include coronary artery bypass graft surgery and percutaneous coronary interventions (PCI). The determination of which revascularization approach is used depends in part on patient presentation and characteristics, primarily severity of CAD (e.g., number of vessels involved, degree of stenosis, SYNTAX [Synergy Between PCI With Taxus and Cardiac Surgery] score), but other factors such as age, diagnosis of diabetes, peripheral vascular disease or heart failure and smoking status also play a role. The SYNTAX score is an assessment of overall coronary lesion complexity, with higher scores representing more complex coronary disease (low scores is defined as ≤ 22 , an intermediate score as 23–32, and a high score ≤ 33).

PCI is an X-ray guided procedure that involves threading a catheter through a major artery to the site of the damaged vessel, and inflating an attached balloon (or other device) to open the affected vessel. A stent may be placed at the damaged site to keep the vessel open. PCI methods have progressed with time, beginning with balloon angioplasty, then bare metal stent placement, and more recently drug eluting stent placement. The drugs in the drug eluting stents (e.g., sirolimus, paclitaxel, zotarolimus, everolimus, and biolimus) inhibit vascular smooth muscle cell proliferation and reduce stent thrombosis and restenosis. To date, relative to medical therapy alone, PCI has not been shown to significantly improve all-cause death, cardiac death or MI, or nonfatal MI in any individual trial, or in meta-analyses of trials when limited to those that exclude patients with recent ACS,⁵³⁻⁵⁵ and may increase the risk of MI in the short-term.⁵⁶⁻⁵⁹ In a recent meta-analysis of eight trials (7229 patients) comparing medical therapy alone with coronary stent placement plus medical therapy in patients with stable CAD (including post-MI), rates of death, nonfatal MI, unplanned revascularization and persistent angina were not found statistically different through a mean of 4.3 years followup.⁶⁰ However, PCI has been shown to reduce symptoms and incidence of angina PCI reduces the incidence of angina. In a study with 10-year followup, 59 percent of patients who underwent PCI were free of angina compared with 43 percent of those treated with medical therapy.⁶¹

CABG, or heart bypass surgery, involves grafting a local or transplanted vein in order to allow blood flow to bypass the damaged vessel(s). This procedure has been shown to improve outcomes in patients with left main coronary artery disease when compared to medical therapy alone. In the most recent trial, 10-year survival rates were similar for CABG versus medical therapy, but rates of MI, repeat revascularization, and a composite endpoint (overall mortality, Q-wave myocardial infarction, or refractory angina that required revascularization) were significantly worse with medical therapy.⁶¹

CABG versus PCI. A recent systematic review that included results from thirteen RCTs and five meta-analyses evaluated the relative effects of the revascularization options in patients with unprotected left main disease (ULMD), multivessel CAD, diabetes mellitus, and left ventricular dysfunction (LVD).⁶² The review concludes that in patients with more complex CAD, CABG results in a lower risk of mortality and a composite outcome (all-cause mortality, MI, stroke, or repeat revascularization) versus PCI with drug eluting stents. Further, PCI resulted in higher rates of revascularization. However, the risk of stroke is higher after CABG than PCI. Consistent with other reports, patients with diabetes have a lower risk of the composite endpoint following CABG versus PCI. Another meta-analysis of individual patient-level data from 10 CAD trials compared CABG PCI (with balloon angioplasty or bare-metal stents) or CABG and found that the 5-year mortality rate was slightly lower following in patients with stable symptoms as well as in those with no history of MI.⁶³

Scope and Key Questions

The objective of this review is to assess the effectiveness of noninvasive technologies for the diagnosis of CAD or dysfunction that results in symptoms attributable to myocardial ischemia in patients who present with signs or symptoms suggestive of CAD, whose condition is considered to be stable, and who have no known history of CAD. The intended focus is on clinical outcomes and clinical pathways following the first diagnostic test performed as result of initial risk assessment (which includes clinical presentation and physical exam, family history of CAD, and findings on resting ECG). Further, this report focuses on established tests for diagnosing CAD. Harms related to both the initial test as well as subsequent testing will be evaluated. Information on traditional measures of accuracy (e.g., sensitivity and specificity) of noninvasive tests versus the historically accepted gold standard of ICA was presented for context in the background.

Key Questions

In stable, symptomatic patients with suspected CAD who do not have previously diagnosed CAD and who have had a resting ECG:

7. For patients considered to be at *very low or low risk* for CAD, what is the comparative effectiveness of **anatomic tests (compared with each other, usual care, or no testing)**:
 - a. For improving primary clinical health outcomes (e.g., quality of life, avoiding myocardial infarction)? In the absence of comparative studies linking testing with outcomes, do the tests predict future clinical events (predictive accuracy)?
 - b. What are the adverse effects, consequences, or harms of testing?
 - c. How do noninvasive tests differ in terms of clinical management based on test results, including referral for coronary angiography or additional noninvasive testing?
 - d. What harms are associated with additional testing following anatomic tests?
 - e. Is there differential effectiveness or harm based on patient characteristics (e.g., sex, age, comorbidities)?

8. For patients considered to be at *very low or low risk* for CAD, what is the comparative effectiveness of **functional tests (compared with each other, usual care, or no testing)**:
 - a. For improving primary clinical health outcomes (e.g., quality of life, avoiding myocardial infarction)? In the absence of comparative studies linking testing with outcomes, do the tests predict future clinical events (predictive accuracy)?
 - b. What are the adverse effects, consequences or harms of testing?
 - c. How do noninvasive tests differ in terms of clinical management based on test results, including referral for coronary angiography or additional noninvasive testing?
 - d. What harms are associated with additional testing following anatomic tests?
 - e. Is there differential effectiveness or harm based on patient characteristics (e.g., sex, age, comorbidities) or the patient's ability to exercise?

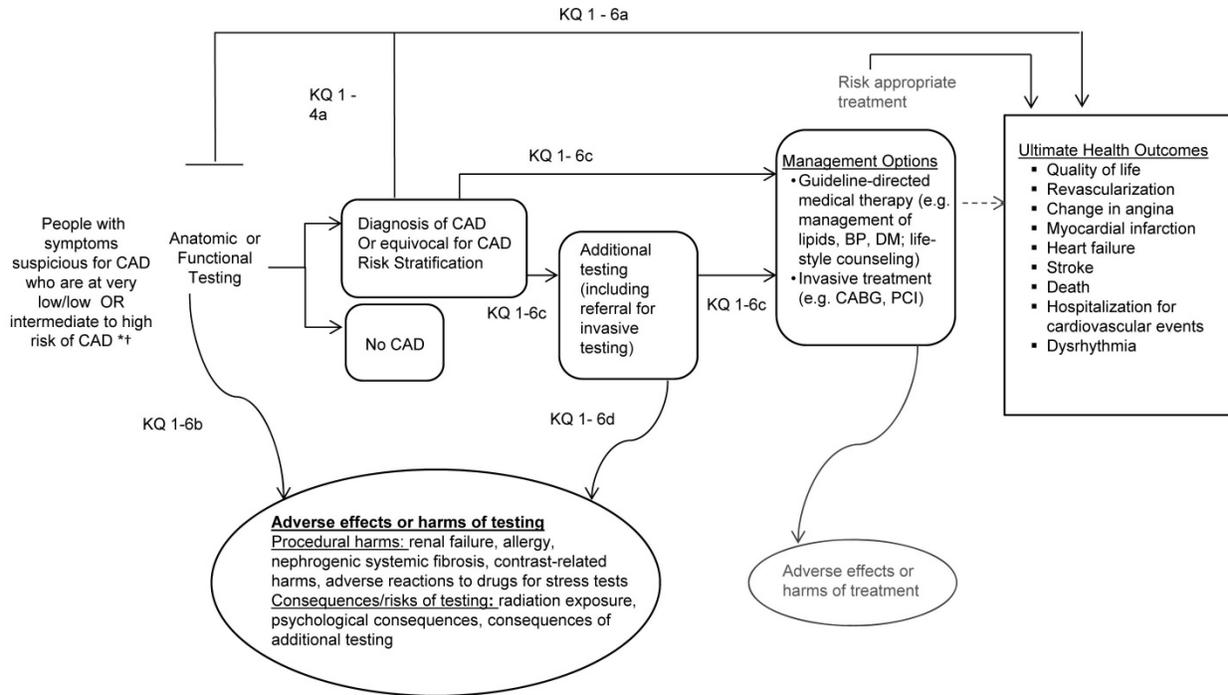
9. For patients considered to be at *intermediate to high risk* for CAD, what is the comparative effectiveness of **anatomic tests (compared with each other usual care, or no testing)**:
- For improving primary clinical health outcomes (e.g., quality of life, avoiding myocardial infarction)? In the absence of comparative studies linking testing with outcomes, do the tests predict future clinical events (predictive accuracy)?
 - What are the adverse effects, consequences, or harms of testing?
 - How do noninvasive tests differ in terms of clinical management based on test results, including referral for coronary angiography or additional noninvasive testing?
 - What harms are associated with additional testing following anatomic tests?
 - Is there differential effectiveness or harm based on patient characteristics (e.g., sex, age, comorbidities)?
10. For patients considered to be at *intermediate to high risk* for CAD, what is the comparative effectiveness of **functional tests (compared with each other, usual care, or no testing)**:
- For improving primary clinical health outcomes (e.g., quality of life, avoiding myocardial infarction)? In the absence of comparative studies linking testing with outcomes, do the tests predict future clinical events (predictive accuracy)?
 - What are the adverse effects, consequences, or harms of testing?
 - How do noninvasive tests differ in terms of clinical management based on test results, including referral for coronary angiography or additional noninvasive testing?
 - What harms are associated with additional testing following anatomic tests?
 - Is there differential effectiveness or harm based on patient characteristics (e.g., sex, age, comorbidities) or the patient's ability to exercise?
11. What is the comparative effectiveness of **anatomic tests versus functional tests** in those who are at *very low or low risk* for CAD?
- For improving primary clinical health outcomes (e.g., quality of life, avoiding myocardial infarction)?
 - What are the adverse effects, consequences or harms of testing?
 - How do noninvasive tests differ in terms of clinical management based on test results, including referral for coronary angiography or additional noninvasive testing?
 - What harms are associated with additional testing following anatomic tests?
 - Is there differential effectiveness or harm based on patient characteristics (e.g., sex, age, comorbidities) or the patient's ability to exercise?
12. What is the comparative effectiveness of **anatomic tests versus functional tests** in those who are at *intermediate to high risk* for CAD?
- For improving primary clinical health outcomes (e.g., quality of life, avoiding myocardial infarction)?
 - What are the adverse effects, consequences or harms of testing?

- h. How do noninvasive tests differ in terms of clinical management based on test results, including referral for coronary angiography or additional noninvasive testing?
- i. What harms are associated with additional testing following anatomic tests?
- j. Is there differential effectiveness or harm based on patient characteristics (e.g., sex, age, comorbidities) or the patient's ability to exercise?

Analytic Framework

The analytical framework for the systematic review is presented in Figure 3.

Figure 3. Analytic framework for noninvasive testing for coronary artery disease



*People at very low or low risk will be evaluated separately from those at intermediate to high risk as possible.

†KQ 1–6e: Potential modifiers related to differential efficacy and/or safety include patient factors (e.g., age, sex), comorbidities, and ability to exercise.

BP = blood pressure; CABG = coronary artery bypass graft; CAD = coronary artery disease; DM = diabetes mellitus; KQ = Key Question; PCI = percutaneous coronary intervention.

Methods

The methods for this Comparative Effectiveness Review (CER) follow the guidance in the Agency for Healthcare Research and Quality (AHRQ) Methods Guide for Effectiveness and Comparative Effectiveness Reviews.⁶⁴

Topic Refinement and Review Protocol

The topic for this comparative effectiveness review was ranked as a priority topic by a panel of stakeholders convened through the Duke Evidence-based Practice Center's Cardiovascular Topic Identification project. The preliminary Key Questions and scope were developed with input from Key Informants representing practicing clinicians, patients, payers, and others with experience in making health care decisions. The Key Questions were posted on AHRQ's Web site for public comment for 4 weeks. Public comments and input from the Technical Expert Panel (TEP) were used to develop the final Key Questions and protocol. The TEP, convened to provide high-level content and methodological guidance to the review process, consisted of experts in cardiology and cardiac diagnostic testing, radiology, internal medicine, and health services research, as well as professional organizations and policy makers. TEP members disclosed all financial or other conflicts of interest prior to participation. The AHRQ Task Order Officer and the investigators reviewed the disclosures and determined that the TEP members had no conflicts of interest that precluded participation.

Both the final topic refinement document and the systematic review protocol, developed prior to initiation of the review, can be found on the AHRQ Web site at <http://effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/>. The protocol is also registered with the PROSPERO international database of prospectively registered systematic reviews (CRD42015022081).

Literature Search Strategy

Search Strategy

A research librarian conducted searches for primary studies in the following databases through November 2014: Ovid MEDLINE®, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews. A search strategy was developed based on an analysis of the medical subject headings (MeSH), terms, and text words of key articles identified *a priori* (the full search strategy is available in Appendix A). Search start dates were not restricted. The reference lists of included articles and relevant review articles were also reviewed. All citations were downloaded and imported into an electronic database (EndNote® X7 Thomson Reuters, Philadelphia, PA). A list of relevant drugs and manufacturers was provided to the Scientific Resource for request of Scientific Information Packets and relevant published and unpublished studies were assessed for inclusion in the final report.

Due to the large number of citations retrieved by our database searches, two experienced team members created a list of search terms using the exclusion criteria in the PICOTS (populations, interventions, comparators, outcomes, timing, and setting) table and applied a systematic search in EndNote® in order to further exclude studies with a high likelihood of not being relevant. The full list of terms and methods used is available in Appendix A. Briefly, citations without abstracts, those not available in English, and certain publication types (case report, narrative review) were excluded. For the remaining citations, titles were searched for

terms related to unequivocally excluded populations (e.g., stent, cardiomyopathy), interventions (e.g., ultrasound, Doppler, screening), and outcomes. The title was chosen as the search field because it should contain only terms most relevant to the purpose of the study. Out of a total of 17,146 citations, 8186 were excluded using this method.

Literature searches will be updated during the public comment and peer review period in order to ensure any new publications that meet our inclusion criteria are incorporated into the final report.

Inclusion and Exclusion Criteria

Criteria for inclusion and exclusion of studies were based on the Key Questions and the PICOTS approach as described in Table 6. Briefly, studies of stable, symptomatic adult patients undergoing their first noninvasive diagnostic test for suspected coronary artery disease (CAD) were sought. Patients with known CAD, prior myocardial infarction (MI), or prior revascularization were excluded. For all Key Questions, the focus was on evidence from comparative studies with the least potential for bias. Noncomparative studies of predictive accuracy were considered if there was a lack of comparative data for a specific diagnostic modality. Interventions of interest included functional tests (i.e., stress electrocardiogram [ECG], stress echocardiography, stress nuclear imaging specifically single photon emission computed tomography [SPECT] and positron emission tomography [PET], and stress magnetic resonance imaging [MRI]) and anatomic imaging (i.e., coronary computed tomography angiography [CCTA], coronary calcium scoring via electron beam or multidetector computed tomography [CT]). Comparators included other noninvasive tests included in the interventions, usual care (as defined by the authors), or no testing. Studies that included technologies that are not widely available or no longer used, or have not been established for the diagnosis of CAD were excluded.

The primary outcomes listed in the PICOTS table (Table 6) were considered to be the most clinically important and were the focus of reporting, decisions for data pooling, and determination of overall strength of evidence. Additional outcomes are reported in the detailed evidence synthesis sections of the Key Questions with a focus on outcomes common across studies. Where applicable and where data were available, results from the index emergency department (ED) visit and the followup period were reported separately. For studies of predictive accuracy, only hard clinical outcomes (i.e., MI, death, composite cardiac outcome, heart failure) were evaluated. For both the initial test and any subsequent downstream testing, the primary safety outcomes were related to harms of testing (e.g., adverse reaction or allergy to contrast or stress agents) and risks and consequences of testing (e.g., radiation exposure). Treatments and outcomes of treatments were not analyzed as they are beyond the scope of this report.

Studies published only as conference abstracts, non-English-language articles, and studies of nonhuman subjects were excluded. Studies had to report original data to be included.

Table 6. Summary of inclusion and exclusion criteria

	Inclusion	Exclusion
Patients	<p>Adult patients (≥18 years of age) with suspected CAD who present with stable (nonemergent) typical or atypical symptoms suspicious for CAD (e.g., chest pain, chest tightness, chest burning, shoulder pain, palpitations, jaw pain, or nonchest pain symptoms, such as dyspnea or worsening effort tolerance) and who are considered to be at very low, low, or intermediate to high risk of CAD based on initial clinical assessment (including resting ECG) prior to first noninvasive test..</p> <p>Special populations and circumstances of interest include:</p> <ul style="list-style-type: none"> • Patients with renal insufficiency, diabetes, LBBB, HIV, or other comorbidities • Women • Those who are/are not able to exercise • Those with atypical symptoms/atypical presentation • Socioeconomic factors • Clinical setting (e.g., emergency department, outpatient clinic) 	<ul style="list-style-type: none"> • Asymptomatic patients • Patients with known CAD • Patients who have had previous revascularization (CABG, PTCA, stenting) • Studies in populations with >20% asymptomatic or with known CAD unless data are stratified by symptom status/CAD status • Patients being evaluated for other cardiac diseases (e.g., valvular disease, etiology of cardiomyopathy) • Patients with unstable angina who have elevated serum cardiac biomarkers, ECG changes, etc.; those with NSTEMI, STEMI, or definite acute coronary syndrome

	Inclusion	Exclusion
Interventions	<p><u>Functional tests</u> (including use of exercise, vasodilator and/or dobutamine as stressor where appropriate)</p> <ul style="list-style-type: none"> • Exercise electrocardiogram without imaging • Exercise/pharmacologic echocardiography (with or without myocardial contrast) • Exercise/pharmacologic radionuclide imaging with SPECT or PET • Pharmacologic stress magnetic resonance imaging <p><u>Anatomic imaging</u></p> <ul style="list-style-type: none"> • Coronary calcium scoring via EBCT or MDCT • CCTA 	<ul style="list-style-type: none"> • Invasive coronary angiography • Screening applications of tests (application of tests to asymptomatic people, those who are being evaluated for noncardiac surgery) • CT (other than CT for calcium scoring): studies not using 64–slice or higher resolution • Testing for conditions other than evaluation of CAD (e.g., arrhythmia, valvular disease) • Technologies that are not widely available or have not been established for the diagnosis of CAD or those being assessed for feasibility (e.g., gene expression testing, Corus CAD by CardioDx, myocardial contrast echocardiography, myocardial strain imaging (post-ischemic shortening as a marker for ischemic memory), coronary FDG PET, BMIPP ischemic memory imaging, transthoracic Doppler FFR, CT-based FFR, MRA, TEE, CT perfusion) • Technologies that are no longer available or no longer widely used (e.g., MUGA, planar nuclear imaging) • Drugs or devices used in testing that are not available in the United States
Comparators	Other noninvasive tests included in the interventions, usual care, or no testing	<ul style="list-style-type: none"> • Invasive coronary angiography • Studies which do not specify components of “usual care” if that is the comparator

	Inclusion	Exclusion
Outcomes	<p><u>Clinical outcomes (primary focus)</u></p> <ul style="list-style-type: none"> • Quality of life • Change in angina (e.g., worsening) • MI • Heart failure • Stroke • Death • Cardiovascular hospitalization for acute coronary syndrome, heart failure, arrhythmias • Dysrhythmia <p>(For studies of predictive accuracy that do not compare tests, only hard clinical outcomes will be evaluated: These are MI, death, heart failure)</p> <p><u>Intermediate outcomes (to be evaluate based on comparative studies only)</u></p> <ul style="list-style-type: none"> • Need for additional testing (including referral for invasive testing) • Clinical decisionmaking and management based on revised risk stratification such as use of guideline-directed medical therapy, including management of lipids, blood pressure and diabetes; counseling related to diet, physical activity, smoking cessation, alcohol use, and management of psychological factors; use of additional therapies to reduce risk of MI and death (e.g., antiplatelet therapy) • Any need for subsequent revascularization (PCI or CABG) <p><u>Harms, risks and consequences of testing (both initial and subsequent testing)</u></p> <ul style="list-style-type: none"> • Harms of testing (renal failure, allergy, nephrogenic systemic fibrosis, contrast-related harms, adverse reaction to medications used for stress testing), vascular complications • Risks and consequences (radiation exposure, psychological consequences of diagnosis, need for additional testing) 	<ul style="list-style-type: none"> • Studies focused on “per-vessel” or “per-segment” analysis without per patient findings • Treatments and outcomes of treatments will not be evaluated
Timing	At time of first noninvasive test for evaluation (other than initial resting ECG)	
Settings	Nonemergent inpatient settings, or ambulatory/ outpatient settings, including emergency department	

	Inclusion	Exclusion
Study Design	<ul style="list-style-type: none"> • High quality systematic reviews with or without meta-analysis • Prospective studies (RCT or observational) directly comparing interventions with comparators based on established diagnostic criteria will be sought. Retrospective studies will be considered if there are insufficient prospective studies and they are at low risk of bias. • Studies of prognosis and decisionmaking will be included if testing results are reported in relation to clinical outcomes and if there is control for confounding as appropriate; studies of predictive accuracy will be considered if they provide clinical outcomes in untreated people. 	<ul style="list-style-type: none"> • Studies of technique or feasibility or reporting only on the technical aspects of testing • Studies exploring prediction models for diagnostic criteria or prognosis • Studies comparing pharmacological agents for stress testing with each other • Studies of serial assessment of one test • Studies with ≤20 patients • Nonsystematic reviews • Narrative reviews • Abstracts, editorials, letters, conference proceedings • White papers • Articles identified as preliminary reports when results are published in later versions • Case series, case reports
Publication Type	<ul style="list-style-type: none"> • Studies published in English in scholarly journals, published health technology assessments, or publicly available FDA reports • Gray literature (e.g., ongoing or unpublished clinical trial data) 	<ul style="list-style-type: none"> • Single site reports from multicenter trials • Duplicate publications of the same study that do not report on unique outcomes or time points

BMIPP = beta-methyl iodophenyl pentadecanoic acid; CABG = coronary artery bypass grafting; CAD = coronary artery disease; CCTA = coronary computed tomography angiography; CT = computed tomography; EBCT = electron beam computed tomography; ECG = electrocardiography; FDA = U.S. Food and Drug Administration; FDG-PET = Fludeoxyglucose (18F) positron emission tomography; FFR = fractional flow reserve; HIV = human immunodeficiency virus; LBBB = left bundle branch block; MDCT = multidetector computed tomography; MI = myocardial infarction; MRA = magnetic resonance angiography; MUGA = multigated acquisition scan; NSTEMI = Non-ST segment elevation acute coronary syndromes; NSTEMI = Non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; PET = positron emission tomography; PTCA = percutaneous transluminal coronary angioplasty; RCT = randomized controlled trial; SPECT = single photon emission computed tomography; STEMI = ST-segment elevation myocardial infarction; TEE = transesophageal echocardiography.

Study Selection

Abstracts for all citations from the literature searches were independently reviewed by two team members and results were recorded in EndNote. All citations found to be potentially appropriate for inclusion by either reviewer underwent full-text review. Each full-text article was independently evaluated for final inclusion by two investigators. For inclusion, both reviewers had to agree that inclusion criteria were met. Differences between reviewers were resolved through consensus and discussion. A record of studies excluded at the full-text level with reasons for exclusion is included in Appendix C.

Data Extraction

The investigative team created a form in Microsoft Excel for abstracting the data elements for the Key Questions. The data abstraction forms were piloted by two members of the team and refinements made as needed. Two staff members were responsible for abstracting demographic information for each study and five experienced team members entered data for the outcomes of

interest. After data extraction, at least one other staff member and one investigator each verified the accuracy and completeness of abstraction for each study included. Discrepancies were resolved by discussion and consensus.

Reviewers extracted information on general study characteristics (e.g., study design, study period, followup, study setting, funding, and authors' conflicts of interest), study patients (patients approached/eligible/enrolled, age, sex, comorbidities, cardiac risk factors, pretest risk for CAD as defined by the authors), intervention arm details (tests evaluated, patients treated, patients with followup, type of stressor used, type of contrast used, definition of a positive test), test results, clinical health and management outcome measures, adverse events, and information related to study quality. Outcome measures and adverse events were prespecified during the creation of the extraction form to maintain consistency in data reporting. However, unique results were added during the abstraction process as needed. Outcomes that occurred during the index ED visit were reported separately from those that occurred during the followup period; however, for some studies it was unclear if the followup period included the index visit. Limited data were extracted from studies of predictive accuracy with a focus on hard clinical outcomes (i.e., MI, death, composite cardiac outcome, and heart failure). An outline of the specific information included in the data extraction forms are available in Appendix D.

Quality (Risk of Bias) Assessment of Individual Studies

Predefined criteria were used to assess the quality (risk of bias) of included randomized controlled trials (RCTs) and observational studies by using clearly defined templates and criteria as appropriate and following guidance from the Agency for Healthcare Research and Quality (AHRQ) *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*.⁶⁴ Assessment of RCTs followed appropriate criteria and methods established in the Cochrane Handbook for Systematic Reviews of Interventions.⁶⁵ Comparative observational studies were assessed for study design features and sources of potential bias. Briefly, the quality of each comparative study was rated based on the following: methods used for randomization (RCTs only, requirement of computer-generated random numbers, random numbers tables, coin toss, or opaque sequentially numbered envelopes), allocation concealment (RCTs only, requirement of sealed opaque envelopes, centralized randomization, on-site computer based system with a randomization sequence that is not readable until allocation, or blocked randomization), intention to treat analysis (RCTs only), independent or blind outcome assessment, patients comparable at baseline on key CAD risk factors, prespecified threshold or definition for a positive test, acceptable attrition ($\leq 20\%$), comparable attrition between treatment groups ($\leq 10\%$ difference between groups), controlling for possible confounding, full reporting on prespecified outcomes.. These criteria and methods were used in concordance with the approach recommended in the chapter, *Assessing the Risk of Bias of Individual Studies When Comparing Medical Interventions*, in the AHRQ Methods Guide *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*, wherein each study was rated as being “good”, “fair” or “poor” quality.⁶⁶ Two investigators independently assessed the quality of each study, and any discrepancies were resolved through discussion and consensus.

Studies rated “good” are considered to have the least risk of bias, and their results are considered valid. Good-quality studies include clear descriptions of the population, setting, interventions, and comparison groups; a valid method for allocation of patients to treatment; low dropout rates and clear reporting of dropouts; appropriate means for preventing bias; and appropriate measurement of outcomes.

Studies rated “fair” are susceptible to some bias, though not enough to invalidate the results. These studies may not meet all the criteria for a rating of good quality, but no flaw is likely to cause major bias. The study may be missing information, making it difficult to assess limitations and potential problems. The fair-quality category is broad, and studies with this rating will vary in their strengths and weaknesses. The results of some fair-quality studies are likely to be valid, while others may be only possibly valid.

Studies rated “poor” have significant flaws that imply biases of various types that may invalidate the results. They have a serious or “fatal” flaw in design, analysis, or reporting; large amounts of missing information; discrepancies in reporting; or serious problems in the delivery of the intervention. The results of these studies are least as likely to reflect flaws in the study design as the true difference between the compared interventions. Studies rated as being poor in quality *a priori* were not excluded, but considered to be less reliable than higher quality studies when synthesizing the evidence, particularly if discrepancies between studies were present.

Each study evaluated was dual-reviewed for quality by two team members. Any disagreements were resolved by consensus. The final risk of quality assessments are described in detail in Appendix I.

Data Synthesis

When adequate data were reported in at least two studies, meta-analysis was conducted in order to provide more precise estimates for outcomes. To determine the appropriateness of conducting meta-analysis, clinical and methodological diversity and assessed statistical heterogeneity were considered. Given the multiple interventions included in this report, a network meta-analysis was planned to estimate the relative effects of interventions that have not been directly compared, and to make full use of both direct and indirect evidence. However, the number of included studies turned out to be very small (two for each comparison) with limited number of comparisons (only CCTA vs. SPECT, and CCTA vs. usual care). Along with heterogeneity across studies, this made network meta-analysis impossible. Therefore, only standard meta-analysis was conducted and only binary outcomes were eligible. The profile-likelihood random-effects model⁶⁷ was used to combine risk differences while incorporating variation among studies. The presence of statistical heterogeneity among the studies was assessed by using the standard Cochran’s chi-square test, and the magnitude of heterogeneity by using the I^2 statistic.⁶⁸

To account for clinical heterogeneity, we stratified analyses by pretest risk. Within each strata, the number of studies was too small for exploring heterogeneity based on any study level characteristics. Sensitivity analyses using risk ratios were conducted to check the robustness of results to the choice of effect measure. Conclusions were generally similar and not separately reported. All analyses were performed using Stata/IC 12.1 (StataCorp, College Station, TX).

Strength of the Body of Evidence

The strength of evidence (SOE) for each primary efficacy/effectiveness and safety outcome described above was initially assessed by one researcher using the approach described in the *AHRQ Methods Guide for Effectiveness and Comparative Effectiveness Reviews*, also available from the AHRQ Web site.^{64,66}

In determining the strength of a body of evidence regarding a given outcome, the following domains are considered:

- Study limitations: the extent to which studies reporting on a particular outcome are likely to be protected from bias; graded as low, medium, or high level of study limitations
- Consistency: the extent to which studies report the same direction of effect for a particular outcome; graded as consistent, inconsistent, or unknown (in the case of a single study)
- Directness: reflects whether the outcome is directly or indirectly related to health outcomes of interest
- Precision: describes the level of certainty of the estimate of effect for a particular outcome and includes consideration of the sample size and number of events; graded as precise or imprecise
- Reporting bias: suspected if there was evidence of selective reporting, otherwise considered to be undetected

A final strength of evidence grade was assigned by evaluating and weighing the combined results of the above domains; final grades are presented in the Discussion, and tables detailing how final grades were determined are available in Appendix J. To ensure consistency and validity of the evaluation, the strength of evidence ratings for all key outcomes were reviewed by the entire team of investigators, and discrepancies were resolved by consensus.

Briefly, bodies of evidence consisting of RCTs started as high strength while bodies of comparative observational studies began as low strength evidence. The strength of the evidence was then downgraded based on the limitations described above. There are also situations where the observational evidence may be upgraded (e.g., very large size of effect), but we found no instances where these could be applied in this body of evidence (see AHRQ's *Methods Guide* for details on upgrading; see also AHRQ's *Methods Guide for Medical Test Reviews*).⁶⁹ The overall grades and their definitions are as follows:

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

Applicability

Applicability of the evidence was considered by examining the characteristics of the patient populations included in studies (e.g., demographic characteristics, presence of relevant cardiac risk factors, pretest risk for CAD); the sample size of the studies; and clinical settings (e.g., outpatient clinic, emergency department) in which the studies are performed, as outlined in the *AHRQ Methods Guide*.^{64, 70} which is also available from AHRQ EHC website at

<http://www.effectivehealthcare.ahrq.gov/ehc/products/272/603/Methods%20Guide--Atkins--01-03-2011KM.pdf>. Variability in the studies may limit the ability to generalize the results to other populations and settings, for example older studies of established tests may not be as applicable in light of advances in technology and short-term outcomes based on immediate decisionmaking in the emergency department may not be generalizable to longer-term outcomes and decisionmaking in the outpatient setting.

Peer Review and Public Commentary

Experts in the diagnosis and treatment of coronary artery disease as well as individuals representing other important stakeholder groups have been invited to provide external peer review of this Comparative Effectiveness Review. Comments and editorial review will also be provided by the AHRQ Task Order Officer. The draft report will be published on the AHRQ Web site for 4 weeks in order to solicit public comments. At the end of this period, the authors will consider both the peer and public review comments and generate a final report. A disposition of comments report detailing the authors' responses to the peer and public review comments will be made available 3 months after AHRQ posts the final report on the public web site.

Results

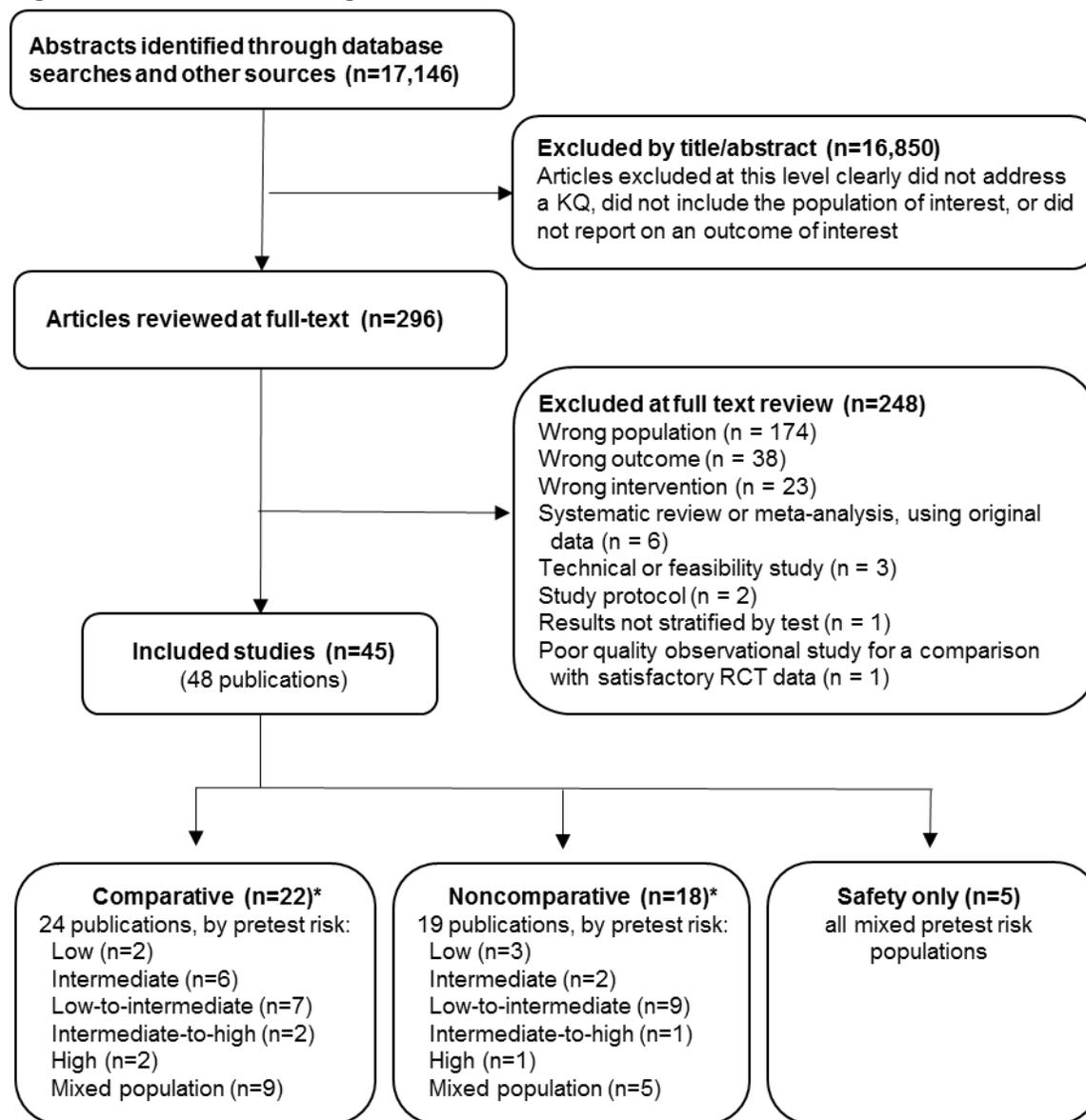
Results of Literature Searches

The results of the literature search and study selection are summarized in the flow chart below (Figure 4). A total of 17,146 potentially relevant citations were identified. After dual review of abstracts and titles, 16,850 articles were excluded. The remaining 296 articles underwent dual review at the full-text level and 45 studies (in 48 publications) met the inclusion criteria and were included in this report: 13 randomized controlled trials (RCTs),⁷¹⁻⁸³ 14 comparative observational studies,⁸⁴⁻⁹⁹ and 18 noncomparative studies.¹⁰⁰⁻¹¹⁸ Of those, 22 studies were designed to compare one noninvasive test to another in separate patient groups and reported our primary outcomes of interest; these studies form the primary basis for our report.

A total of 14 studies compared coronary computed tomography angiography (CCTA) with either usual care (4 RCTs,^{71, 76, 77, 79} 1 prospective observational^{86, 88}); various functional testing (1 RCT)⁷²; single photon emission computed tomography (SPECT) (3 RCTs^{73, 74, 80}, 1 retrospective observational⁸⁴); or with exercise electrocardiography (ECG) (2 RCTs^{75, 78}, 1 retrospective observational,⁹⁴ 1 administrative database⁹⁶). Three studies compared SPECT with exercise ECG (2 RCTs,^{81, 83} 1 administrative database⁹⁶). A total of four studies compared stress echocardiography with either exercise ECG (1 RCT,⁸² 1 prospective observational,⁹⁰ 1 administrative database⁹⁶) or SPECT (1 administrative database).⁹⁶ Only one prospective registry was identified that investigated positron emission tomography (PET) scanning which was compared with SPECT.^{87, 89} No comparative studies of magnetic resonance imaging (MRI) or calcium scoring that met our inclusion criteria were found. CCTA was only anatomic test for which we found comparative data. No other relevant test comparisons were identified. A list of included studies can be found in Appendix B.

A total of 248 articles that did not meet one or more of the inclusion criteria were excluded after full-text review. Appendix C provides a list of these articles with reasons for exclusion (also see Figure 2 below). The primary reason for exclusion (70% of citations) was that studies did not include the population of interest (i.e., no known history of coronary artery disease [CAD]).

Figure 4. Flow chart showing results of literature search



*Some studies were included in more one than one risk strata or reported outcomes for more than one comparison or test of interest.

KQ = Key Question; RCT = randomized controlled trial.

Organization of Results

Given the heterogeneity in how pretest risk was measured and defined across the studies (see Appendix Tables E40-41 for details), results could not be reported as delineated by the Key Questions into distinct pretest risk groups (i.e., low risk and intermediate to high risk). Therefore, the results were organized by pretest risk as defined by the study authors, which included low-risk, intermediate-risk, low- to intermediate- risk, intermediate- to high-risk, high-risk, and mixed-risk populations (or pretest risk not reported). Studies describing “high” pretest risk excluded patients with acute coronary syndrome (ACS) and were interpreted as representing the higher risk end of the intermediate pretest risk range. Available data from studies conducted in emergency departments (EDs) were primarily for the index ED visit and is noted. Outcomes such as MI at the time of the ED index visit were considered to reflect diagnosis of MI at that time. Where available, data on longer term followup is presented.

For each section, within the specified pretest risk categories, key points were presented followed by detailed information from evidence synthesis for the following test comparisons, presented in this order: anatomic testing (CCTA or calcium scoring via CT) versus usual care; functional testing versus functional testing (any combination of the following: stress echocardiography, stress ECG, stress echocardiography, SPECT, PET, or MRI); and anatomic testing versus functional testing (any comparison of tests from the above categories). Following a brief description of the study populations, detailed results are reported in terms of clinical outcomes, clinical management outcomes, harms of index and additional testing, and differential effectiveness or safety in subgroups. Limited evidence from noncomparative studies reporting on predictive accuracy is included at the end of each risk category only for tests for which there was no or little comparative data available.

Low Pretest Risk of Coronary Artery Disease

Key Points

Given the focus of the report on evaluation of testing based on pretest risk, results for the low pretest risk groups are presented below even though evidence from these groups was rated as insufficient.

CCTA Versus Usual Care

- In a small subgroup of low-risk patients presenting to the ED, there was insufficient evidence from one fair-quality trial to draw conclusions regarding differences between CCTA and usual care in all-cause mortality or hospitalization for acute coronary syndrome through 30 days. At the index ED visit, frequency of ICA referral and revascularization was similar (insufficient evidence).

SPECT Versus Exercise ECG

- In a small subgroup of low-risk outpatients, there was insufficient evidence from one fair-quality trial that SPECT patients had less additional noninvasive stress testing than exercise ECG patients through a mean of 22 months. SPECT patients were slightly more likely to have ICA referral through the same followup period (insufficient evidence), although the difference was not statistically significant.

Detailed Synthesis

A total of five studies were identified in populations with a low pretest risk of CAD and two included the following comparisons: CCTA versus usual care (1 RCT)⁷¹ and SPECT versus exercise ECG (1 RCT)⁸¹ (Table 7); three additional noncomparative studies (4 publications) reported on the predictive accuracy of stress echocardiography.^{100, 105, 110, 111}

Anatomic Tests Versus Usual Care

CCTA Versus Usual Care

One fair-quality trial compared CCTA with usual care in low risk patients (Appendix Tables E1–E3, E10–E13, E18–E21, E36, G3, G4); no other studies compared anatomical testing with usual care in this population. The trial enrolled 266 patients presenting with chest pain to a single ED in South Korea.⁷¹ Study funding was not reported. Results were stratified based on pretest risk, with 99 of the 266 patients at low pretest risk. CCTA was performed with 64-slice scanning in 50 low risk patients; usual care consisted of a conventional diagnostic strategy (e.g., serial ECGs, cardiac biomarkers) and was used in 49 low risk patients. Subsequent diagnostic tests were done at the discretion of the treating physician. Overall, groups were similar in age (mean 57.5 years), sex (38.7% female), and cardiac risk factors, however these characteristics were not compared for low risk patients only. Methodological shortcomings included unclear randomization method, allocation concealment, and blinding of outcomes assessment.

Clinical outcomes. No deaths occurred in either group through 1 month of followup; MI occurred similarly between groups at the index visit (4% in both groups).⁷¹ The frequency of hospital admissions at the index visit was similar between groups in terms of those for acute coronary syndrome (6% in both groups) and total admissions (14% for CCTA versus 16% for usual care). Patients in the CCTA group were less likely to have an unnecessary hospital admission at the time of the index visit (0% versus 6%), though this result did not achieve statistical significance (RD -6, 95% CI -13 to 0.6 per 100). Clinical outcomes based on test results were not reported.

Clinical management. ICA referral at the index visit was similar following CCTA versus usual care (6% versus 10%, RD -4, 95% CI -15 to 7 per 100), as was revascularization (6% versus 2%, RD 4, 95% CI -4 to 12 per 100).⁷¹ Noninvasive stress testing was done in 80% of usual care patients but data on noninvasive stress testing were not reported for the CCTA group. Revascularization at the index visit was similar between CCTA and usual care groups (6% versus 2%, RD 4, 95% CI -4 to 12 per 100).

Harms of index test and consequences of index and additional testing; differential effectiveness or safety in subgroups. Not reported for low risk patients.

Functional Tests Versus Functional Tests

SPECT Versus Exercise ECG

One fair-quality trial compared SPECT with exercise ECG in low risk patients (Appendix E, Tables E1–3, E10–E13, E18–E21, E36–E40, G3); no other studies compared different types of functional testing in this population.⁸¹ The trial included 457 patients referred for stable chest pain to a single outpatient center in the United Kingdom; funding grants were received from Bristol-Myers Squibb and Northwick Park Cardiac Research, as well as from an individual. Results were stratified based on pretest risk; 71 patients had low pretest likelihood of CAD.

Patients underwent either SPECT (n=27) or exercise ECG (n=44). Treadmill exercise was employed in both groups; pharmacological stress was employed in some patients receiving SPECT. Groups were similar overall in age (mean age 59 years), sex (43.5% female), and cardiac risk factors but were not compared within the low risk group. Patients were followed for a mean of 22 months; loss-to-followup was not reported. Methodological shortcomings included unclear randomization method, allocation concealment, and blinding of outcomes assessment.

Clinical outcomes. Not reported for low risk patients.

Clinical management. SPECT recipients had a slightly higher frequency of ICA referral compared with exercise ECG over a mean of 22 months followup in low risk patients (7% versus 0%), although the difference did not achieve statistical significance (RD 7 per 100, p=0.07). This trial used Bayesian methods to model posttest risk and reported that 86 percent of those with low pretest risk finished with low posttest risk (SPECT 78% vs. ECG 91%) and that those with a normal or low risk test in either arm did not receive ICA. SPECT was associated with less additional imaging than was exercise ECG (0 versus 13.6%), with a risk difference of -14 per 100 (95% CI -24 to -4). Medication therapy based on the initial test was statistically similar between SPECT and exercise ECG patients (92.6% versus 86.3%, RD 6, 95% CI -8 to 20 per 100).

Harms of index test and consequences of index and additional testing; differential effectiveness or safety in subgroups. Not reported for low risk patients.

Noncomparative Studies: Functional

No noncomparative studies of anatomical testing in patients at low risk met the inclusion criteria that reported outcomes of interest. For functional testing in this population, only studies of stress echocardiography were identified.

Stress echocardiography. Three noncomparative studies of stress echocardiography in low pretest risk patients reported on predictive accuracy, two of which were conducted in an ED setting. Stressors included exercise or dobutamine in one trial^{110, 111} and two used exercise only.^{100, 105} Studies sizes ranged from 149 to 1618 patients. In terms of test-positive patients, cardiac events occurred in no patients through 6 months in one ED study, and in 3 to 5 percent of patients through a median of 36 months (outpatient setting) or a mean of 54 months (ED setting) followup, respectively. The frequency of any cardiac event in those who tested negative was 1 per 100 people in all studies (Appendix F, Tables F1–F2).

Table 7. Summary of findings and strength of evidence: Low pretest risk

Outcome*	Comparison	Number of Studies (N)	Setting	Conclusions	Strength of Evidence
Mortality (all-cause)	CCTA vs. usual care†	1 RCT (n=99 in low-risk subgroup)	ED	No deaths through 1 month in either group. Definitive conclusions are not possible.‡	Insufficient
Invasive Coronary Angiography Referral	CCTA vs. usual care†	1 RCT (n=99 in low-risk subgroup)	ED	Similar frequency of referral (CCTA 6% vs. usual care 10%) at index visit (RD -4, 95% CI -15 to 7 per 100, p=NS). Definitive conclusions are not possible.‡	Insufficient
	SPECT vs. exercise ECG	1 RCT (n=68 in low-risk subgroup)	Outpatient	Somewhat more common following SPECT (7%) versus exercise ECG (0%) through a mean of 22 months (RD 7 per 100, p=0.0690). Definitive conclusions are not possible.‡	Insufficient
Revascularization	CCTA vs. usual care†	1 RCT (n=99 in low-risk subgroup)	ED	Revascularization at the index visit was similar between CCTA (6%) and usual care (2%) (RD 4, 95% CI -4 to 12 per 100, p=NS). Definitive conclusions are not possible.‡	Insufficient
Additional Testing	SPECT vs. exercise ECG	1 RCT (n=68 in low-risk subgroup)	Outpatient	SPECT was associated with less subsequent stress testing with imaging than exercise ECG through a mean of 22 months (0% vs. 14%, respectively) (RD -14, 95% CI -24 to -4 per 100). Definitive conclusions are not possible.‡	Insufficient
Hospitalization (Cardiac related)	CCTA vs. usual care†	1 RCT (n=99 in low-risk subgroup)	ED	Hospitalization for ACS was similar for CCTA and usual care groups (4% vs. 2%). Definitive conclusions are not possible.‡	Insufficient

ACS = acute coronary syndrome; CCTA = coronary computed tomography angiography; CI = confidence interval; ECG = electrocardiography; ED = emergency department; NS = not statistically significant; RCT = randomized controlled trial; RD = risk difference; SPECT = single photon emission computed tomography.

*Primary outcomes not listed in this table had no evidence and thus insufficient strength of evidence.

†Usual care consisted of a conventional diagnostic strategy using serial ECGs and cardiac biomarkers.

‡Definitive conclusions are not possible due to lack of data from subgroup analyses in RCTs.

Intermediate Pretest Risk of Coronary Artery Disease

Key Points

Evidence for all primary outcomes and comparators not listed below was insufficient to draw conclusions due to study limitations and/or imprecision in the observational study or due to lack of evidence.

CCTA Versus Usual Care

- In intermediate-risk patients presenting to the ED, there was low-strength evidence from two fair-quality trials that patients in the CCTA and usual care groups had similar mortality, MI, any revascularization, PCI, CABG, or additional testing at the index ED visit and through 28 to 30 days. ICA referral was also similar at the index visit and after the index visit through 28 days (low strength of evidence).

SPECT Versus Exercise ECG

- In intermediate-risk women (setting not reported) groups were similar with respect to mortality, ICA referral, revascularization, and hospitalization through 24 months based on one fair-quality trial (low strength of evidence). However, moderate strength of evidence from this trial suggests that SPECT is associated with less additional noninvasive testing than exercise ECG.
- A second fair-quality trial on the general population reported that in a subgroup of intermediate-risk outpatients, SPECT was associated with less referral to ICA (low strength of evidence) and additional stress testing (low strength of evidence) through a mean of 22 months of followup.
- Differences in patient characteristics between the two trial may partially explain differences in findings; One trial was comprised of women with a mean age of 63 years who were able to perform ≥ 5 METS on the Duke Activity Status Index. Findings from the other trial are based on subanalysis of intermediate risk patients from a general population of >50 percent men with mean age of 59 years old with any activity ability.

CCTA Versus Functional testing

- In intermediate-risk outpatients, moderate-strength evidence suggested that all-cause mortality, nonfatal MI, and cardiac hospitalizations were similar between groups through 12 months and a median of 25 months based on one good-quality trial. There was high strength of evidence that CCTA was associated with more ICA referrals and revascularizations (including CABG and PCI evaluated separately) through 90 days. Major procedural complications were similar between groups (moderate strength of evidence).

Detailed Synthesis

A total of eight studies were identified in populations with an intermediate pretest risk of CAD and six (7 publications) included the following comparisons: CCTA versus usual care (2 RCTs,^{71,76} 1 prospective observational^{86,88}), CCTA versus various functional testing (1 RCT),⁷² and SPECT versus exercise ECG (2 RCTs)^{81,83} (Table 8); two additional noncomparative studies reported on the predictive accuracy of coronary artery calcium scoring (CACS).^{116,118}

Anatomic Tests Versus Usual Care

CCTA Versus Usual Care

Two fair-quality trials compared CCTA with usual care in patients with intermediate pretest risk (Appendix Tables E1–E3, E10–E13, E18–E21, E36, E40, G3, G4).^{71,76} One large trial enrolled 1000 intermediate risk patients with chest pain across nine emergency departments (EDs) in the United States.⁷⁶ The trial was funded by grants from the National Institutes of Health and from the National Heart, Lung, and Blood Institute. Patients underwent testing with 64-slice (or higher) CCTA (n=501) or usual care (n=499) which employed the standard evaluation strategy used at each ED. One trial of chest pain patients presenting to a single ED in South Korea stratified results according to pretest risk; 111 (of 266 total) patients were categorized as having intermediate pretest probability of ACS.⁷¹ Study funding was not reported. Patients were tested with 64-slice CCTA (n=55) or usual care (n=56) which consisted of a conventional diagnostic strategy using serial ECGs and cardiac biomarkers. Subsequent

diagnostic tests were done at the discretion of the treating physician. Within each trial, the CCTA and usual care groups were similar in age, sex, and cardiac risk factors. However, the two trials differed somewhat in overall patient characteristics. The study by Chang et al. 2008 included slightly older patients (mean age 58 vs. 54 years), more males (61% vs. 53%), and fewer people with hypertension (44% vs. 54%) or dyslipidemia (27% vs. 45%) compared with the Hoffman et al. 2012 study. Neither study provided a baseline risk score for their population. Methodological shortcomings included unclear randomization method and allocation concealment (Chang et al. 2008), lack of a prespecified definition of a positive test (Hoffmann 2012, et al.), and unclear blinding of outcomes assessment (both trials).

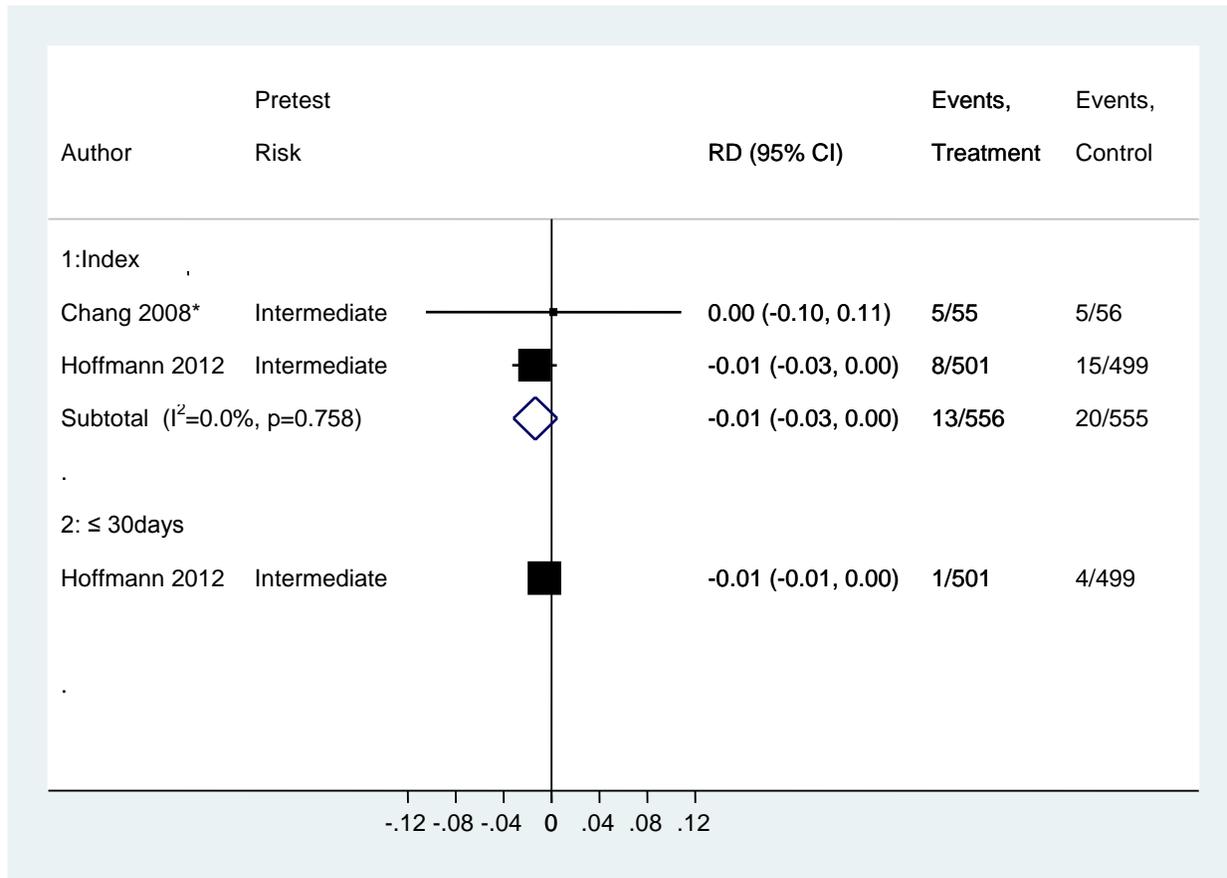
One poor-quality prospective observational study compared CCTA with usual care in 200 patients at intermediate pretest risk (according to the Thrombolysis in Myocardial Infarction [TIMI] risk score; scores/mean not reported), with relevant results published in two separate papers.^{86,88} The study was conducted in a single emergency department in Germany; funding was not reported. Patients received CCTA testing (n=100) or usual care (n=100) to include repeated biomarker measurements, stress testing (e.g., exercise ECG, stress echocardiography, SPECT), and clinical observation. Patients in the CCTA group were younger (mean age 58 vs. 66 years) and more likely to be female (48% vs. 39%) than those in the usual care group; cardiac risk factors were similar between groups. Methodological shortcomings included unclear blinding of outcomes assessment and lack of controlling for baseline differences between groups

Clinical outcomes. No deaths were reported in either of the two trials during the 1 month followup periods. MI diagnosis at the index visit occurred with similar frequency in CCTA and usual care patients across both trials (2.3% vs. 3.6%, pooled RD -1, 95% CI -3 to 0 events per 100 patients, $I^2=0\%$) (Figure 5).^{71,76} After the index visit and through 28 days of followup, one trial also found that MI was similar both CCTA (0.2%) and usual care groups (0.8%) (RD -0.6, 95% CI -1.5 to 0.3 events per 100 people).⁷⁶ Across both trials, diagnosis with unstable angina at the index visit was more common in the CCTA group (9.0%) compared with the usual care group (5.4%) (pooled RD 4, 95% CI 1 to 6 per 100 people, $I^2=0\%$) (Figure 6).^{71,76} Through 28 days followup (and after the index visit), one trial reported similar incidences of unstable angina requiring PCI (0.2% vs. 0.4%; RD -0.2, 95% CI -0.9 to 0.5 per 100).⁷⁶ In the smaller trial, hospital admission for acute coronary syndrome at the time of the index ED visit was similar between the CCTA and usual care groups (36% vs. 32%, RD 4, 95% CI -13 to 22 per 100 patients).⁷¹ The larger trial found that CCTA was associated with significantly fewer hospitalizations at the index visit compared with usual care (51.9% vs. 82.3%, RD -33, 95% CI -39 to -28 per 100 patients),⁷⁶ but the smaller trial found no difference between groups (RD -8, 95% CI -27 to 10 per 100 patients).⁷¹ Considerable statistical heterogeneity across the for the pooled estimate (RD -22, 95% CI -47 to 2 per 100 patients, $I^2=85.1\%$) is noted and may in part be due to differences in patient characteristics between the two studies as well as available sample size in one trial (Figure 7).^{71,76} The smaller trial found that CCTA was associated with fewer unnecessary hospital admissions (defined as an admission for a medical condition that should not have led hospitalization) compared with usual care (4% vs. 20%, RD -16, 95% CI -28 to -4 per 100 patients).⁷¹ Admittance to the observation unit at the index visit was significantly less common in the CCTA group (31%) versus the usual care group (60%), with 30 fewer patients per 100 being admitted (95% CI -36 to -24 per 100).⁷⁶

The single observational study reported no major adverse cardiovascular events in either group through 3 months followup, including death, myocardial infarction, unstable angina requiring hospitalization, or development or progression of heart failure requiring

hospitalization.^{86, 88} They report that hospitalization for recurrent chest pain was slightly less frequent in CCTA versus usual care patients (0% vs. 3%, RD -3, 95% CI -6 to 0.3 per 100 patients) through the 3-month followup period.

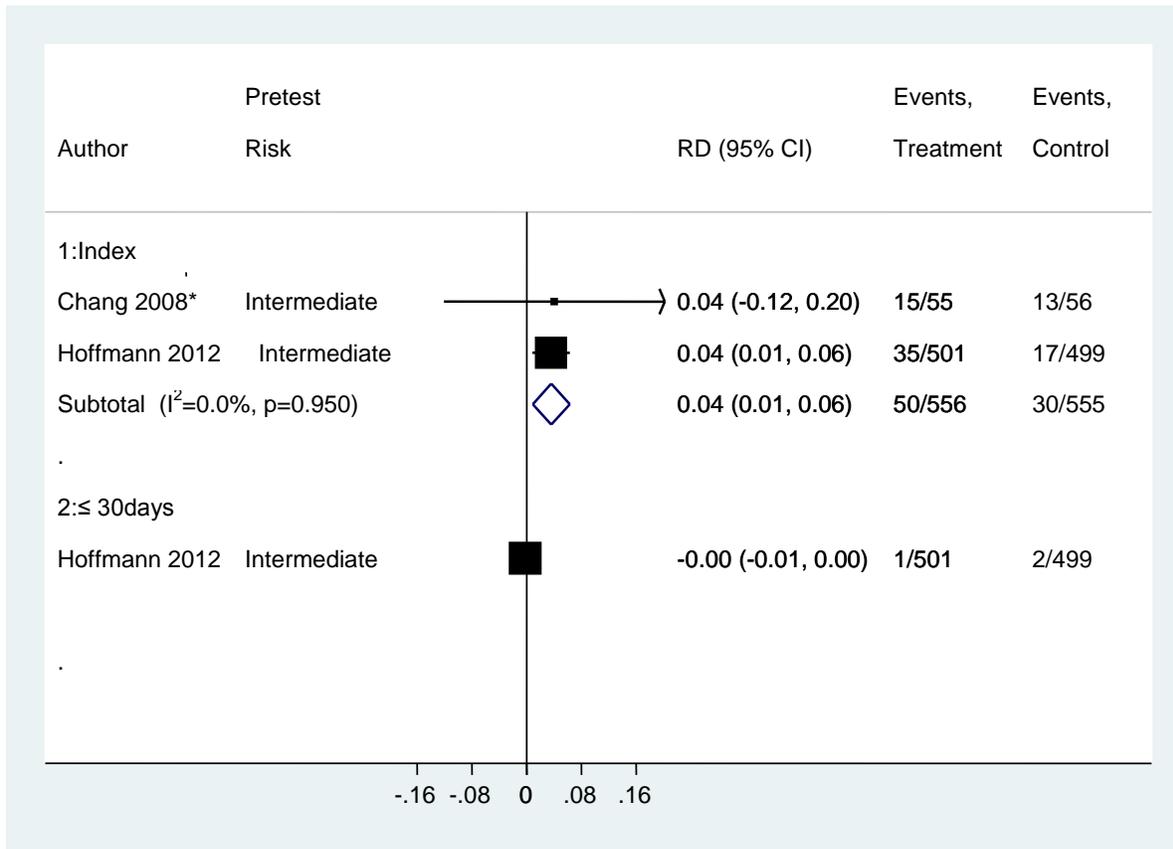
Figure 5. Meta-analysis results for risk of myocardial infarction across studies comparing CCTA with usual care in patients with intermediate pretest risk



CCTA = coronary computed tomography angiography; CI = confidence interval; RD = risk difference.

*Subgroup of intermediate-risk patients.

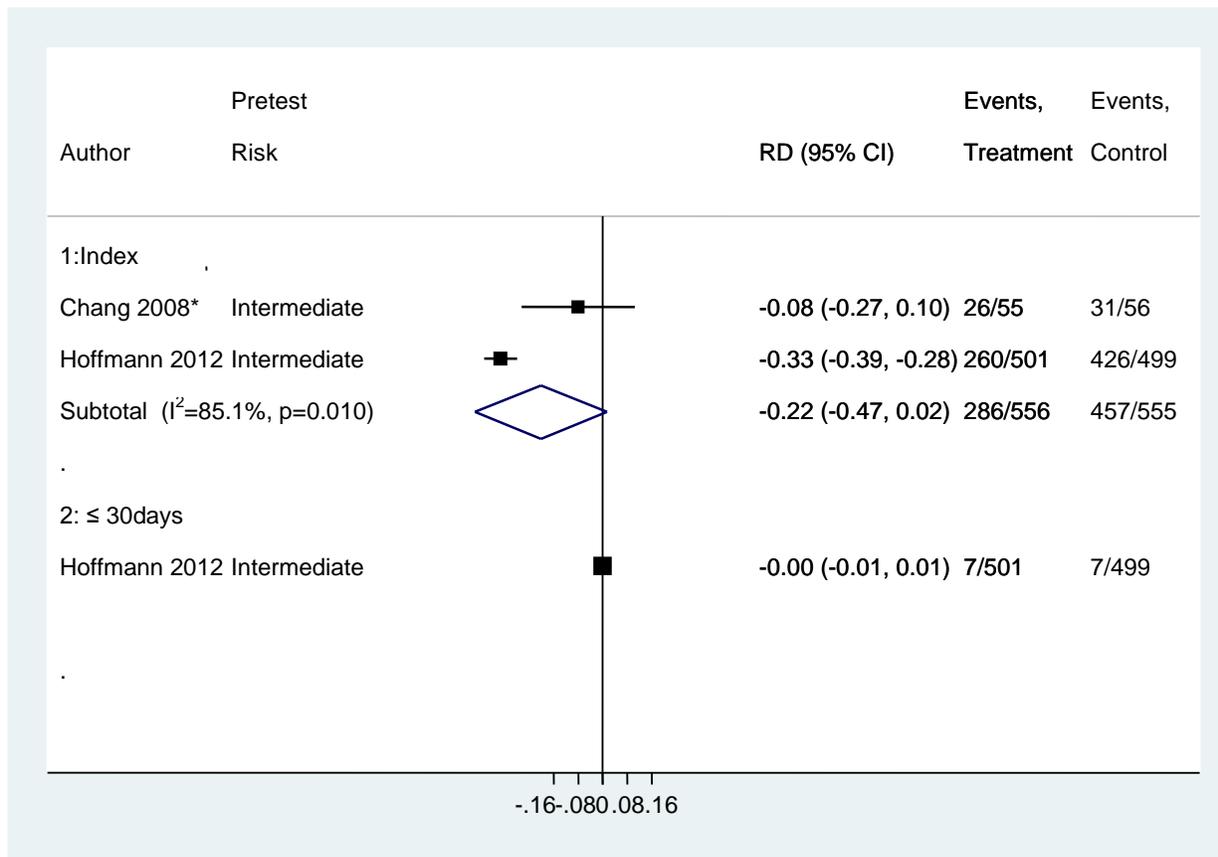
Figure 6. Meta-analysis results for risk of unstable angina across studies comparing CCTA with usual care in patients with intermediate pretest risk



CCTA = coronary computed tomography angiography; CI = confidence interval; RD = risk difference.

*Subgroup of intermediate-risk patients.

Figure 7. Meta-analysis results for risk of hospital admission across studies comparing CCTA with usual care in patients with intermediate pretest risk



CCTA = coronary computed tomography angiography; CI = confidence interval; RD = risk difference.

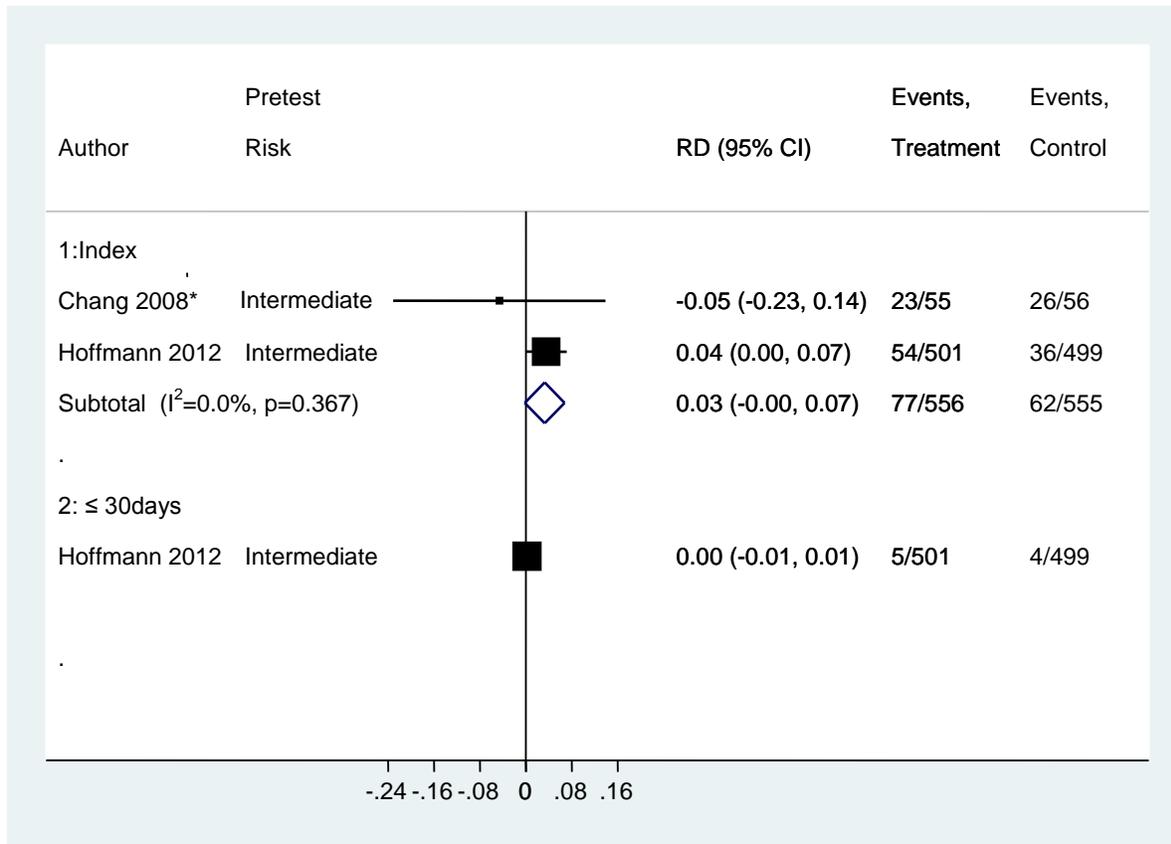
*Subgroup of intermediate-risk patients.

Clinical management: Referral to ICA at the index visit occurred with similar frequency in the CCTA group compared with the usual care group based on data from both trials (13.8% vs. 11.2%, RD 3, 95% CI 0 to 7 per 100 patients, $I^2=0\%$) (Figure 8),^{71, 76} as well as during the 28-day period following the index visit in the larger trial (1.0% for CCTA vs. 0.8% for usual care).⁷⁶ The latter trial reported that patients receiving CCTA testing were significantly less likely to receive any of three types of stress testing at the index ED visit compared with the usual care group: SPECT (10% vs. 25%, RD -15, 95% CI -19 to -10 per 100 patients); stress echocardiography (4% vs. 20%, RD -16, 95% CI -20 to -13 per 100 people); or exercise treadmill testing (2% vs. 29%, RD -27, 95% CI -31 to -23 per 100 patients). The protocol of that trial called for stress testing only as a second test in the CCTA group, but as the first test in the usual care group. In the 28 days after the index ED visit, percentages of patients in the CCTA and usual care groups who received these noninvasive stress tests were similar: SPECT (1.6% vs. 1.8%), stress echocardiography (0% in both groups), or exercise treadmill testing (2% vs. 3%). In the smaller trial, 50% of intermediate risk usual care patients underwent additional stress testing at the time of the index ED visit however this data was not reported for intermediate risk CCTA patients.⁷¹ Revascularization (PCI or CABG) at the index visit was similar between the CCTA (7.2%) and usual care (5.6%) groups at the time of the index ED visit compared with the

usual care group based on data from both trials (RD 2, 95% CI -1 to 5 per 100 patients, $I^2=0\%$) (Figure 9).^{71, 76} One trial similarly reported comparable proportions of patients who had PCI at the index visit (5.0% vs. 2.8%, RD 2.0, 95% CI -0.3 to 4.3 per 100 patients) and through 28 days of followup after the index ED visit (0.6% in both groups); CABG was performed in 1.0% patients in both groups at the index visit and no patients in either group received CABG during the followup period.⁷⁶

The observational study reported no statistical differences between CCTA and usual care patients in PCI (9% vs. 15%), CABG (1% vs. 2%), and intensified medical therapy (7% vs. 8%); however, the rate of referral for ICA was significantly lower following CCTA (19% vs. 87%; RR 0.22, 95% CI 0.14 to 0.33).^{86, 88} Of those referred, a smaller proportion of CCTA patients showed no obstructive CAD on ICA compared with patients tested via usual care: 10.5% (2/19) vs. 71.3% (62/87); RR 0.15, 95% CI 0.04 to 0.55.

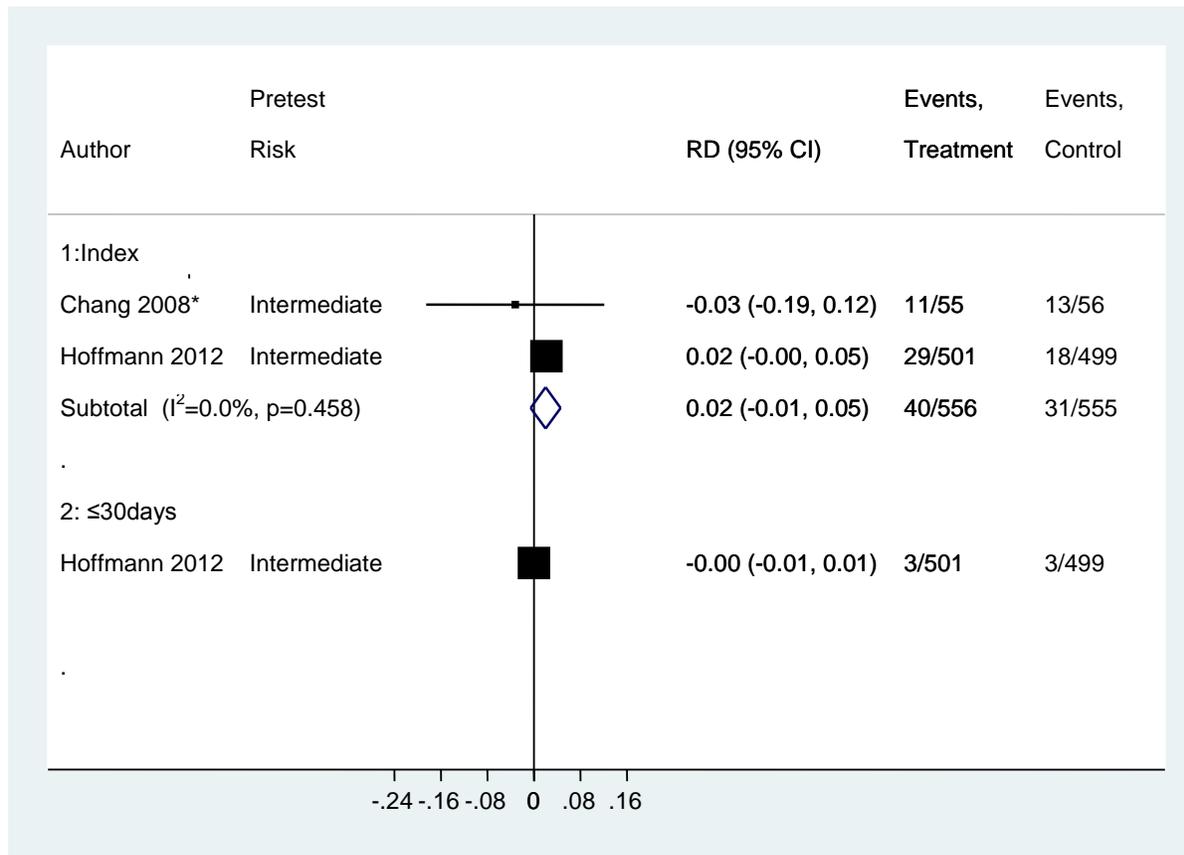
Figure 8. Meta-analysis results for risk of invasive coronary angiography across studies comparing CCTA with usual care in patients with intermediate pretest risk



CCTA = coronary computed tomography angiography; CI = confidence interval; RD = risk difference.

*Subgroup of intermediate-risk patients.

Figure 9. Meta-analysis results for risk of any revascularization across studies comparing CCTA with usual care in patients with intermediate pretest risk



CCTA = coronary computed tomography angiography; CI = confidence interval; RD = risk difference.

*Subgroup of intermediate-risk patients.

Harms of index test and consequences of testing. The larger RCT reported a similarly low incidence of periprocedural complications (not defined further) in the CCTA (0.4%) and the usual care (0%) groups.⁷⁶ In this same trial, CCTA was associated with significantly higher exposure to radiation at the index visit compared with usual care (mean 13.9 ± 10.4 vs. 4.7 ± 8.4 mSv, $p < 0.001$). The observational study reported a mean radiation exposure of 8.7 mSv following CCTA but did not report exposure for the usual care group.^{86, 88}

Harms of additional testing. Cumulative radiation exposure (index visit plus additional testing during followup) was significantly greater following CCTA compared with usual care as reported by one RCT (mean 14.3 ± 10.9 vs. 5.3 ± 9.6 mSv, $p < 0.001$)⁷⁶; however, over the followup period, the effective radiation dose was similar between groups: 0.4 versus 0.6 mSv, respectively.

Differential effectiveness or safety in subgroups. No analyses related to differential effectiveness or safety of CCTA versus usual care with regard to patient characteristics or other factors were provided.

Functional Tests Versus Functional Tests

SPECT Versus ECG

Two fair-quality trials compared SPECT with exercise ECG in intermediate risk patients (Appendix Tables E1–E3, E10–E13, E18–E21, E36–E40, G3); no other studies compared different types of functional testing in this population. One large RCT (N=824) enrolled women only who were at intermediate pretest risk presenting with chest pain to various outpatient cardiology practices (43 sites) across the United States and Canada.⁸³ The trial was funded by a grant from GE Healthcare. The women received either SPECT (n=412) or exercise ECG (n=412); the Bruce exercise protocol was used in both test groups. Overall, groups were similar in age (median 62 years), presenting symptoms (60% typical angina), and cardiac risk factors. Outcomes were reported at 24 months for 93.7% of patients. Another RCT included 457 patients referred for stable chest pain to a single outpatient center in the United Kingdom; funding via grants was received from Bristol-Myers Squibb and Northwick Park Cardiac Research, as well as from an individual.⁸¹ Results were stratified based on pretest risk; 280 patients had intermediate pretest likelihood of CAD. Patients underwent either SPECT (n=178) or exercise ECG (n=102). Treadmill exercise was employed in both groups; pharmacological stress was used in some patients receiving SPECT. Groups were similar overall in age (mean age 59 years), sex (43.5% female), and cardiac risk factors but were not compared within the intermediate risk group. Neither study reported a baseline risk score for their population. Patients were followed for a mean of 22 months; loss to followup was not reported for this subgroup of patients but was 3% attrition in the overall population. Methodological shortcomings included lack of concealed allocation in both studies, and lack of blinded assessment of outcomes in one.⁸¹

Clinical outcomes. All clinical outcomes are reported through 24 months followup in the trial of women. Overall mortality was similarly low in both SPECT and exercise ECG groups (1.0% vs. 0.5%),⁸³ as was the frequency of major adverse cardiac events (including cardiac death, nonfatal myocardial infarction, or hospitalization for acute coronary syndrome or heart failure) (2.3% SPECT) versus 1.7% (exercise ECG), RD 0.54, 95% CI -1.5 to 2.6 per 100 people). Hospitalizations for chest pain (3.9% vs. 3.1%) and worsening angina frequency or stability (5% of patients in both groups) were also similar. By 12 months, 49 percent of patients in both groups were angina-free, and by 24 months a similar proportion of patients in both groups remained free from angina (SPECT 64.9% vs. ECG 60.4%; RD 4.5, 95% CI -2.3 to 11.4 per 100 patients).

Clinical management. While referral to ICA was similar between the SPECT and exercise ECG arms (5.7% vs. 6.4%, RD -0.7, 95% CI -4 to 3 per 100 people) through 24 months in the trial of women,⁸³ the other trial reported that a significantly smaller percentage of subjects undergoing SPECT had ICA when compared to ECG testing (10.7% vs. 43.1% RD -32.5, 95% CI -43 to -22 per 100 people) through a mean of 22 months.⁸¹ This latter trial used Bayesian methods to model posttest risk and reported that only 21 percent of those with intermediate pretest risk finished with intermediate posttest risk (SPECT 2% vs. ECG 53%) and that those with a normal or low risk test in either arm did not receive ICA. Based on results from the Shaw trial of women, additional testing with SPECT was done less frequently in the SPECT group than in the exercise ECG group (9.1% vs. 18.6%, RD -8.9, 95% CI -13.7 to -4.1 per 100 people); of those randomized to SPECT, this test was repeated in 9, 8, and 15 percent of women with normal, mildly abnormal, and moderately to severely abnormal results, while among those randomized to exercise ECG, the frequency of crossover to SPECT (counts as use of additional

test) was 8, 25, and 43 percent respectively for women who had normal, indeterminate, and abnormal ECG results.⁸³ Additional testing with exercise ECG was performed in 0.3% of patients in both groups. In the other trial, SPECT patients had significantly less additional testing when compared to ECG testing through a mean of 22 months (0% vs. 38%, RD -38; 95% CI -48 to -29 per 100).⁸¹ Revascularization was similar between SPECT and exercise ECG in the trial of women only (2.1% vs. 1.0%, RD 1.1, 95% CI -0.7 to 2.8 per 100 patients).⁸³ The trial of the general population reported that SPECT patients were considerably more likely to receive medical therapy than those who underwent stress ECG (89.3% vs. 18.6%, RD 70.7, 95% CI 61.9 to 79.5 per 100).⁸¹

Harms of index test and consequences of testing. The Shaw trial reported a mean radiation exposure of 14.0 mSv following SPECT but did not report radiation exposure for the exercise ECG group.⁸³

Harms and consequences of additional testing; differential effectiveness or safety in subgroups. Not reported for intermediate risk patients.

Anatomic Tests Versus Functional Tests

CCTA Versus Functional Testing (various)

One large, good-quality trial compared CCTA with functional testing in 10,003 outpatients at intermediate pretest risk (Appendix E, Tables E22–E25, E40, G3);⁷² no other studies compared anatomical with functional testing in this population. Dubbed the PROMISE trial, this multicenter RCT was conducted in 193 outpatient clinics (cardiology, radiology, primary care, urgent care, and anesthesiology departments) across the United States and Canada. Outcomes were reported at 12 months for 93.5 percent of patients; outcomes at the last followup were also reported (median of 25 [interquartile range (IQR) 18 to 34] months). CCTA scans were obtained with a 64-detector row scanner and contrast. Those randomized to functional testing could undergo one of a number of different testing modalities which were chosen prior to randomization. Functional testing modalities used included nuclear stress imaging (63.09%), stress echocardiography (21.09%), and exercise ECG (9.53%). A similar proportion of patients randomized to both CCTA and functional testing (6.25%) did not receive the assigned test (i.e., did not undergo any test or underwent a different test). The stressors used for nuclear imaging and echocardiography were not reported.

For inclusion, patients were required to have new or worsening symptoms consistent with suspected CAD, no history of MI, and no history revascularization or testing within the past 12 months. In general, males were required to be 55 years or older and females 65 years or older, although exceptions were made for slightly younger patients with specific risk factors. The two groups were well-balanced in terms of baseline characteristics and cardiac risk factors (mean of 2.4 ± 1.1 risk factors per patient). Mean age was 60.8 ± 8.3 years and 52.7% of patients were female. Racial or ethnic minorities comprised 22.6% of the population. Pretest risk for CAD was intermediate (10%–90%) in 92.6% of patients (and was low [$<10\%$] in 2.5% and high [$>90\%$] in 4.9%). Overall, the mean pretest risk of CAD was $53.3\% \pm 21.4\%$ based on a combined Diamond and Forrester and Coronary Artery Surgery Study score. Presenting symptoms included chest pain (72.7%) and shortness of breath on exertion (14.9%). Angina was atypical in the majority of patients (77.7%), with fewer presenting with typical (11.7%) or nonanginal pain (10.6%). There were no apparent methodological shortcomings.

Clinical outcomes. There was no difference in the risk of all-cause death between the CCTA and functional testing groups through 12 months (0.42% vs. 0.64%) and a median of 25 months (1.48% vs. 1.50%) followup.⁷² Similarly, risk of nonfatal MI was similar between groups through 12 months (0.36% vs. 0.54%, RD -0.18, 95% -0.44 to 0.08 per 100 people) and a median of 25 months (0.60% vs. 0.80%, RD -0.20, 95% CI -0.53 to 0.13 per 100). However, the composite risk of death or nonfatal MI was significantly lower in the CCTA group through 12 months (0.78% vs. 1.14%, adjusted HR 0.66, 95% CI 0.44 to 1.00, p=0.049) although the difference was no longer significant by a median of 25 months (2.08% vs. 2.24%). The primary composite endpoint (defined as all-cause death, nonfatal MI, hospitalization for unstable angina, or a major procedural complication (stroke, major bleeding, anaphylaxis, renal failure requiring dialysis)) or the secondary endpoint (defined as the primary endpoint or catheterization showing no obstructive CAD) both occurred similarly in both groups. While there was no difference in hospitalization for unstable angina between groups through 12 months (0.98% vs. 0.67%), it was more common in the CCTA group through a median of 25 months (1.22% vs. 0.82%, RD 0.40, 95% CI 0.01 to 0.80 per 100 patients). In contrast, hospitalization for any cardiovascular reason other than unstable angina was less common in the CCTA group through a median of 25 months (0% vs. 0.10%, p=0.0255). There was no difference between groups at either timepoint in composite outcome of death, nonfatal MI, or hospitalization for unstable angina. While the study reported that a similar percentage of patients in each test group tested positive (abnormal) (10.68% vs. 1.16%), clinical outcomes were not stratified according to test result.

Clinical management. Although more patients in the CCTA group underwent ICA within 90 days compared with the functional testing group (12.19% vs. 8.11%, RD 4.08, 95% CI 2.90 to 5.26 per 100 people), the ICA results showed no obstructive CAD (i.e., false positives) in fewer CCTA patients (27.9% vs. 52.5% of patients who underwent ICA; p<0.0001). Moreover, more CCTA patients underwent revascularization within 90 days than functional testing patients (6.22% vs. 3.16%, RD 3.07, 95% CI 2.24 to 3.90 per 100 patients); similar results were found when considering the 90-day risk of CABG alone (1.44% vs. 0.76%, RD 0.68, 95% CI 0.27 to 1.09 per 100) and PCI alone (4.8% vs. 2.4%, RD 2.4, 95% CI 1.7 to 3.1 per 100 people).⁷²

Harms of index test and consequences of testing. Douglas et al. reported no difference between CCTA and functional imaging groups in the risk of major procedural complications, which was a component of the primary outcome and included stroke, major bleeding, anaphylaxis, or renal failure requiring dialysis (0.1% in both groups) throughout the entire followup period.⁷² There was similar risk of procedural stroke (0.02% vs. 0.04%) and major bleeding (0.1% in both groups) between groups, and no instances of anaphylaxis or renal failure requiring dialysis. Exercise-induced hypotension, stress-induced symptoms not resolved within 20 minutes, ventricular tachycardia, and hemodynamic instability were rare, occurring in no CCTA patients and less than 0.1% of functional testing patients; it was unclear whether these events occurred peri-procedurally or at a later timepoint. There were no cases of rapid atrial fibrillation that did not slow or convert. Mild contrast reactions were significantly more common in the CCTA group than in the functional testing group (0.4% vs. 0%, RD 0.44 per 100, p<0.0001). The study reported a total of 37 mild safety events in the CCTA group and 21 in the functional testing group, making these events significantly more common for CCTA patients (0.74% vs. 0.42%, RD 0.32, 95% CI 0.02 to 0.62 per 100 people, p=0.0344).

Harms of additional testing. In the PROMISE trial (Douglas et al.), cumulative radiation exposure through 90 days was higher in the CCTA group compared with the functional testing group (mean 12.0 ± 8.5 vs. 10.1 ± 9.0 mSv (mean difference, 3.0, 95% CI 2.7 to 3.3)).⁷²

Differential effectiveness or safety in subgroups. Douglas et al. reported that none of the prespecified subgroups modified the primary composite outcome (all-cause death, nonfatal MI, hospitalization for unstable angina, or a major procedural complication (stroke, major bleeding, anaphylaxis, renal failure requiring dialysis)), with results across subgroups consistent with those for the entire study population. Subgroups examined included age (<65 vs. ≥65 years), sex, race (white vs. nonwhite), pretest risk assessment (≤30% vs. 31-70% vs. >70%), CAD equivalence, and pretest probability of CAD (low [<10%] vs. intermediate [10-90%] vs. high [>90%]).⁷²

Noncomparative Studies: Anatomical

No noncomparative studies of functional testing in patients at intermediate risk met the inclusion criteria that reported outcomes of interest. For anatomic testing in this population, only studies of coronary artery calcium scoring were identified.

Calcium scoring. Two noncomparative studies of calcium scoring during CCTA in patients at intermediate pretest risk reported on predictive accuracy.^{116, 118} One study was conducted in a single center outpatient setting (N=341) and the other included data from an international, multicenter registry (N=10,037). The study populations differed, respectively, in terms of mean age (62 vs. 57 years) and sex (33% vs. 43% female), as well as several cardiac risk factors. The followup period was 24 months in both studies. In terms of test-positive patients, the frequency of any cardiac event was substantially higher in both studies (5 and 8 per 100 people) compared with those who tested negative (0 and 1 per 100). The registry study also reported a higher risk of both mortality (1.8% vs. 0.4%) and myocardial infarction (1.1% vs. 0.2%) in those who tested positive (Appendix F, Tables F3–F4).

Table 8. Summary of findings and strength of evidence: Intermediate pretest risk

Outcome*	Comparison	Number of Studies (N)	Setting	Conclusions	Strength of Evidence
Mortality (all-cause)	CCTA vs. Usual Care†	2 RCTs (N=1098)‡ 1 observational (N=200)	ED	There is low strength of evidence that a difference in mortality was not found. At ED visit through 28 to 30 days, there were no deaths in either group (2 RCTs). Through 3 months followup, there were no deaths in either group (observational study).	Low
	SPECT vs. Exercise ECG	1 RCT (N=824 women)	NR	There is low strength of evidence that a difference in mortality was not found. Through 24 months, overall mortality was similarly low in both groups (1.0% vs. 0.5%).	Low
	CCTA vs. Functional Testing	1 RCT (N=10,003)	Outpatient	Mortality was similar between the CCTA and functional testing groups through 12 months (0.42% vs. 0.64%) and a median of 25 months (1.48% vs. 1.50%) followup.	Moderate

Outcome *	Comparison	Number of Studies (N)	Setting	Conclusions	Strength of Evidence
Myocardial Infarction	CCTA vs. Usual Care [†]	2 RCTs (N=1098) [‡] 1 observational (N=200)	ED	Strength of evidence is low that a difference in diagnosis of MI was not found (2.3% vs. 3.6%, pooled RD -1, 95% CI -3 to 0 events per 100 patients, I ² =0%) (2 RCTs) at the index ED visit; or after index visit through 28 days (0.2% vs. 0.8%, RD -0.6, 95% CI -1.5 to 0.3 events per 100 people) in one trial (N=987). The observational study reported no MIs in either group through 3 months followup.	Low
	CCTA vs. Functional Testing	1 RCT (N=10,003)	Outpatient	Nonfatal MI was similarly rare between groups through 12 months (0.36% vs. 0.54%, RD -0.18, 95% -0.44 to 0.08 per 100 people) and a median of 25 months (0.60% vs. 0.80%, RD -0.20, 95% CI -0.53 to 0.13 per 100 people).	Moderate
Heart Failure	CCTA vs. Usual Care [†]	1 observational (N=200)	ED	Through 3 months followup, there was no development or worsening of heart failure that required hospitalization in either group. Definitive conclusions are not possible. [§]	Insufficient
Invasive Coronary Angiography Referral	CCTA vs. Usual Care [†]	2 RCTs (N=1098) [‡]	ED	At the index visit, ICA referral was similar in the testing groups (13.8% vs. 11.2%, RD 3, 95% CI 0 to 7 per 100 patients, I ² =0%, p=NS). Through 28 days followup (after the index visit), there was no difference between groups (1.0% vs. 0.8%) in one RCT (N=987).	Low
	SPECT vs. Exercise ECG	2 RCTs (N=824 women in one trial; n=280 in intermediate-risk subgroup in other trial)	NR (trial of women) Outpatient (general population)	One trial of women only reported identical referral rates for ICA in both groups (6%) through 24 months. The other trial (general population) found that SPECT was associated with a significantly lower risk of ICA (10.6% vs. 43.1%, RD -32, 95% CI -43 to -22 per 100) through a mean of 22 months followup.	Low
	CCTA vs. Functional Testing	1 RCT (N=10,003)	Outpatient	ICA within 90 days was significantly more common in the CCTA group than the functional testing group (12.19% vs. 8.11%, RD 4.08, 95% CI 2.90 to 5.26 per 100 people).	High
Revascularization	CCTA vs. Usual Care [†]	2 RCTs (N=1098) [‡]	ED	At the index visit, revascularization was similar between CCTA (7.2%) and usual care (5.6%) (pooled RD 2, 95% CI -1 to 5 per 100 patients, I ² =0%) (2 RCTs).	Low
	SPECT vs. Exercise ECG	1 RCT (N=824 women)	NR	Similar over 24 months of followup in the SPECT (2.0%) and exercise ECG groups (1.0%) in one trial of women only (RD 1.1, 95% CI -0.7 to 2.8 per 100 patients).	Low

Outcome *	Comparison	Number of Studies (N)	Setting	Conclusions	Strength of Evidence
	CCTA v vs. Functional Testing	1 RCT (N=10,003)	Outpatient	Significantly more CCTA patients underwent revascularization within 90 days than functional testing patients (6.22% vs. 3.16%, RD 3.07, 95% CI 2.24 to 3.90 per 100 people).	High
Percutaneous Coronary Intervention	CCTA vs. Usual Care [†]	1 RCT (N=987) 1 observational (N=200)	ED	Similar rates of PCI at the index ED visit (5% vs. 3%) (1 RCT), through 28 days (0.6% vs. 0.6%) (1 RCT), and through 3 months (9% vs. 15%) (1 observational study).	Low
	CCTA vs. Functional Testing	1 RCT (N=10,003)	Outpatient	More common following CCTA versus functional testing through 90 days (4.8% vs. 2.4%, RD 2.4, 95% CI 1.7 to 3.1 per 100 people).	High
Coronary Artery Bypass Graft	CCTA vs. Usual Care [†]	1 RCT (N=987) 1 observational (N=200)	ED	Similar between groups at the index visit (1% in both groups) (1 RCT), through 28 days (0% in both groups) (1 RCT), or through 3 months (1% vs. 2%) (1 observational study).	Low
	CCTA vs. Functional Testing	1 RCT (N=10,003)	Outpatient	More common following CCTA versus functional testing through 90 days (1.44% vs. 0.76%, RD 0.68, 95% CI 0.27 to 1.09 per 100 people).	High
Additional Testing	CCTA vs. Usual Care [†]	1 RCT (N=987)	ED	Through 28 days (and after the index visit) similar frequency of additional noninvasive testing: SPECT (1.6% vs. 1.8%); stress echocardiography (0% in both groups) or exercise treadmill testing (2% vs. 3%).	Low
	SPECT vs. Exercise ECG	2 RCTs (N=824 women in one trial; n=280 in intermediate-risk subgroup in other trial)	NR (trial of women) Outpatient (general population)	SPECT was associated with a significantly lower risk of additional noninvasive testing in both trials; this included stress testing with or without imaging in one RCT of women only (9.4% vs. 18.6%; RD -9, 95% CI -14 to -4 per 100). The other trial reported additional stress testing in no SPECT patients and 38% of exercise ECG patients (RD -38, 95% CI -48 to -29 per 100).	Moderate (trial of women) Low (subgroup of general population)
Hospitalization (Cardiac related)	CCTA vs. Usual Care [†]	1 RCT (N=987) 1 observational (N=200)	ED	Strength of evidence is low that hospitalizations were similar at the time of ED index visit (pooled RD -22, 95% CI -47 to 2 per 100 patients, I ² =85.1%); the larger trial (N=987) found fewer hospitalizations with CCTA versus usual care (51.9% vs. 82.3%, RD -33, 95% CI -39 to -28 per 100 patients) but the smaller trial (N=111) found no difference between groups. The observational study found that through 3 months, hospitalization for recurrent chest pain was similar (0% vs. 3%, RD -3, 95% CI -6 to 0.3 per 100 patients, p=NS).	Low

Outcome *	Comparison	Number of Studies (N)	Setting	Conclusions	Strength of Evidence
	SPECT vs. Exercise ECG	1 RCT (N=824 women)	NR	Through 24 months, hospitalization for chest pain was similarly low between groups (3.9% vs. 3.1%, RD 0.8, 95% CI -1.8 to 3.4).	Low
	CCTA vs. Functional Testing	1 RCT (N=10,003)	Outpatient	Through a median of 25 months, no difference was found between groups in the risk of cardiac hospitalization (1.22% vs. 0.92%, RD -0.30, 95% CI -0.10 to 0.71 per 100 people), and hospitalization for unstable angina was similar but significantly more common in CCTA patients (1.22% vs. 0.82%, RD 0.40, 95% CI 0.01 to 0.80 per 100).	Moderate
Harms of the Index Test	CCTA vs. Functional Testing	1 RCT (N=10,003)	Outpatient	For major procedural complications, there were no differences between groups (procedural stroke (0.02% vs. 0.04%); major bleeding (0.1% in both groups); no cases of anaphylaxis or renal failure requiring dialysis). Overall, minor side effects (e.g., stress-induced symptoms, mild contrast reactions) occurred similarly between groups although the difference was statistically significant (0.74% vs. 0.42%, RR 1.77, 95% CI 1.05 to 3.01).	Moderate

CABG = coronary artery bypass graft; CCTA = coronary computed tomography angiography; CI = confidence interval; ECG = electrocardiography; ED = emergency department; ICA = invasive coronary angiography; MI = myocardial infarction; NS = not statistically significant; PCI = percutaneous coronary intervention; RCT = randomized controlled trial; RD = risk difference; RR = relative risk; SPECT = single photon emission computed tomography.

*Primary outcomes not listed in this table had no evidence and thus insufficient strength of evidence.

†Usual care varied by study and included consisted of the standard evaluation strategy used at each ED (1 RCT), a conventional diagnostic strategy using serial ECGs and cardiac biomarkers (1 RCT), and repeated biomarker measurements, stress testing (e.g., exercise ECG, stress echocardiography, SPECT), and clinical observation (observational study).

‡Number of patients includes the 987 patients in the Hoffman trial and the subset of 111 patients who were at intermediate pretest risk in the Chang trial.^{71, 76}

§Definitive conclusions are not possible due to study limitations and/or imprecision in observational studies.

Low To Intermediate Pretest Risk of Coronary Artery Disease

Key Points

Evidence for all primary outcomes and comparators not listed below was insufficient to draw conclusions due to study limitations and/or imprecision in the observational study or due to lack of evidence.

CCTA Versus Usual Care

- In low- to intermediate-risk patients presenting to the ED, there is low strength of evidence showing no difference between groups in mortality or MI diagnosis at the index visit or through 1 month based on one fair-quality trial. Moderate strength of evidence from the same trial suggests that CCTA patients were less likely to be hospitalized at the index ED visit but cardiac-related hospitalizations through 1 month were similar. The

CCTA groups were less likely to undergo additional testing at the index and 1-month followup visits (one fair-quality trial) and through 3-months followup (one poor-quality trial) (moderate [1 month] and low [3 months] strength of evidence). While ICA referrals were similar for the groups at the index ED visit and through 1- to 3-month followup, there were slightly more revascularization procedures in the CCTA group at the index visit in one large fair-quality trial but no difference through the followup period across two trials (low strength of evidence).

CCTA Versus Exercise ECG

- In low- to intermediate-risk patients, there was low strength of evidence that differences were not found in mortality or MI between groups through 12 months based on one trial of ED patients and one observational study of outpatients (both fair-quality). The 12-month rate of referral to ICA and revascularization was significantly greater following CCTA than exercise ECG based on data from the trial of ED patients (low strength of evidence).

CCTA Versus SPECT

- In low- to intermediate-risk patients presenting to the ED, there is low strength of evidence from two trials (one good- and one fair-quality) that no difference was found between groups in mortality through 6 months. There was moderate strength of evidence that there was no difference in MI (both RCTs) or cardiac-related hospitalizations (1 good-quality RCT) through 6 months; one fair-quality observational study of outpatients also reported no difference in mortality or cardiac-related hospitalizations between groups through a mean of 30 months. Together, the trials of ED patients reported that ICA referrals were similar between groups at both the index ED test and through 6 months (low strength of evidence). Additional noninvasive testing was more common following CCTA at the index visit (high strength of evidence from two trials); additional noninvasive testing through 6 months was similar (low strength of evidence from one trial). Moderate strength of evidence from both trials of ED patients suggests similar referral for revascularization, including PCI and CABG evaluated separately, at the index visit and through 6 months.

Detailed Synthesis

A total of 14 studies were identified in populations with low to intermediate pretest risk of CAD and seven included the following comparisons: CCTA versus usual care (2 RCTs),^{77, 79} SPECT (2 RCTs,^{73, 74} 1 retrospective observational⁸⁴), and exercise ECG (1 RCT,⁷⁵ 1 retrospective observational⁹⁴) (Table 9); seven additional noncomparative studies (2 of which contained data for two different tests) reported on the predictive accuracy of stress echocardiography (2 studies),^{102, 106} exercise ECG (4 studies),^{101-103, 108} and calcium scoring (3 studies).^{103, 112, 114}

Anatomic Tests Versus Usual Care

CCTA Versus Usual Care

Two RCTs, one fair-quality⁷⁷ and one poor quality,⁷⁹ compared CCTA with usual care in patients with low to intermediate pretest risk presenting with chest pain to the emergency

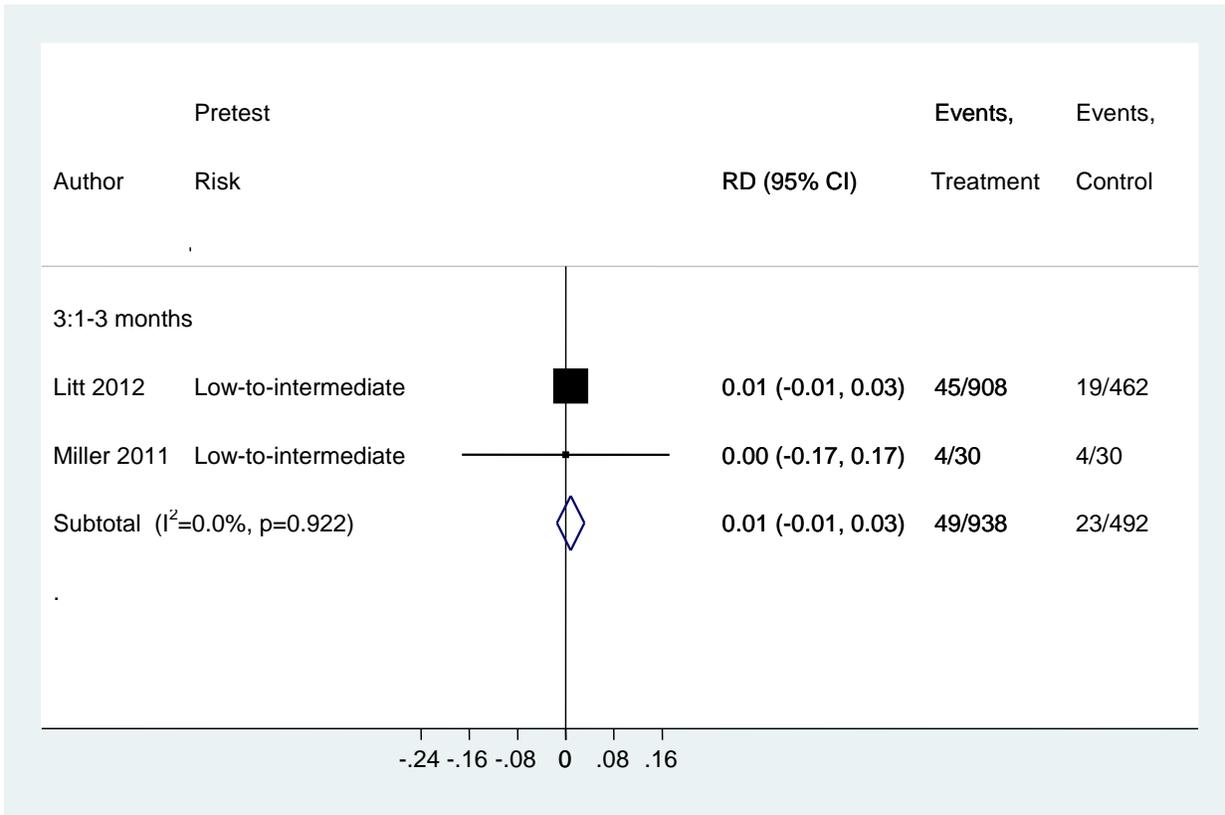
department (ED) in the United States (Appendix E, Tables E28–E31, E40, E42, G3)^{77, 79}; no other studies compared anatomical testing with usual care in this population. In one large multicenter trial conducted across five EDs, patients received testing with 64-slice (or higher) CCTA with contrast (n=908) or usual care (n=462) consisting of traditional “rule out” approaches at the discretion of the patients’ treating physician (64% underwent diagnostic testing, primarily stress testing with imaging).⁷⁷ Outcomes were reported at the index visit and at 1 month; only 84.5 percent of patients randomized to CCTA actually underwent the test. This trial was supported by the Commonwealth of Pennsylvania Department of Health and the American College of Radiology Imaging Network Foundation. A small RCT was conducted in a single ED and all patients received standard treatment (i.e., 12-lead ECG, coronary biomarkers, continuous ECG monitoring, medication, cardiology consultation, and additional cardiac testing as required) with those randomized to the intervention group also undergoing 64-slice CCTA (n=30 in both groups).⁷⁹ Outcomes were reported for all patients over a 3-month followup period. This trial received grants from the National Center for Research Resources. Within each trial, the CCTA and usual care groups were similar in age and sex; cardiac risk factors were also similar between groups in one study⁷⁷ but not reported in the second.⁷⁹ Only one of the trials reported baseline risk scores; 51, 36 and 13 percent of the overall population had a TIMI risk score of 0, 1, and 2 or higher, respectively.⁷⁷ Across trials, mean ages (49 vs. 51 years) and the proportion of females (53% vs. 50%) were similar. The trial by Litt et al. 2012 enrolled more African Americans (60% vs. 47%) as compared with Miller et al. 2012 trial. Methodological shortcomings included unclear allocation concealment and unclear blinding of outcomes assessment in both studies and no reporting of or adjustment for standard cardiac risk factors in one.⁷⁹

Clinical outcomes. In the larger trial, no deaths were reported for CCTA or usual care patients during the 30-day followup period.⁷⁷ The same trial found similar percentages of patients with a MI diagnosis at the index ED visit (1.0% vs. 0.9%, RD 0.1, 95% CI -0.9 to 1.2 per 100 people) and through 30 days (1.1% in both groups). At the index visit, diagnosis with acute coronary syndrome without MI was also similar between CCTA and usual care groups (3.1% vs. 1.5%, RD 1.6, 95% CI -0.01 to 3.2 per 100 patients); CCTA was associated with significantly more positive diagnoses for CAD (9.0% vs. 3.5%, RD 5.6, 95% CI 3.1 to 8.1 per 100).⁷⁷ The CCTA group was less likely than the usual care group to be admitted to the hospital or observation unit at the index ED visit (50% vs. 77%, RD -26.8, 95% CI -31.9 to -21.8 per 100), with similar incidences between the groups of cardiac-related hospital admissions after the index visit (3.1% vs. 2.4%, RD 0.7, 95% CI -1.1 to 2.6).⁷⁷ In the smaller trial, the CCTA group was less likely to be hospitalized (for presumably any reason) during the 90-day followup period compared with the usual care group (20% vs. 53%, RD -33, 95% CI -56 to -10 per 100), but it was not clear whether or not this included admissions at the time of the index visit.⁷⁹ This same trial found that ED visits within 90 days were less common in the CCTA group compared with the usual care group, though the results did not reach statistical significance (17% vs. 33%, RD -17, 95% CI -38 to 5 per 100 people),⁷⁹ while similar proportions of CCTA and usual care patients had revisits to the ED during 30 days of followup as reported in the larger trial (8.0% vs. 7.2%, RD 0.5, 95% CI -2.5 to 3.5).⁷⁷ The smaller trial found no significant difference between the CCTA and usual care groups in change in quality of life, as measured by either the SF-12 Physical Component Score or the SF-12 Mental Component Score.⁷⁹

Clinical management. ICA referral was similar between CCTA and usual care patients at both the index ED visit (4.1% vs. 3.9%) as reported by the larger trial (4.1% vs. 3.9%),⁷⁷ and

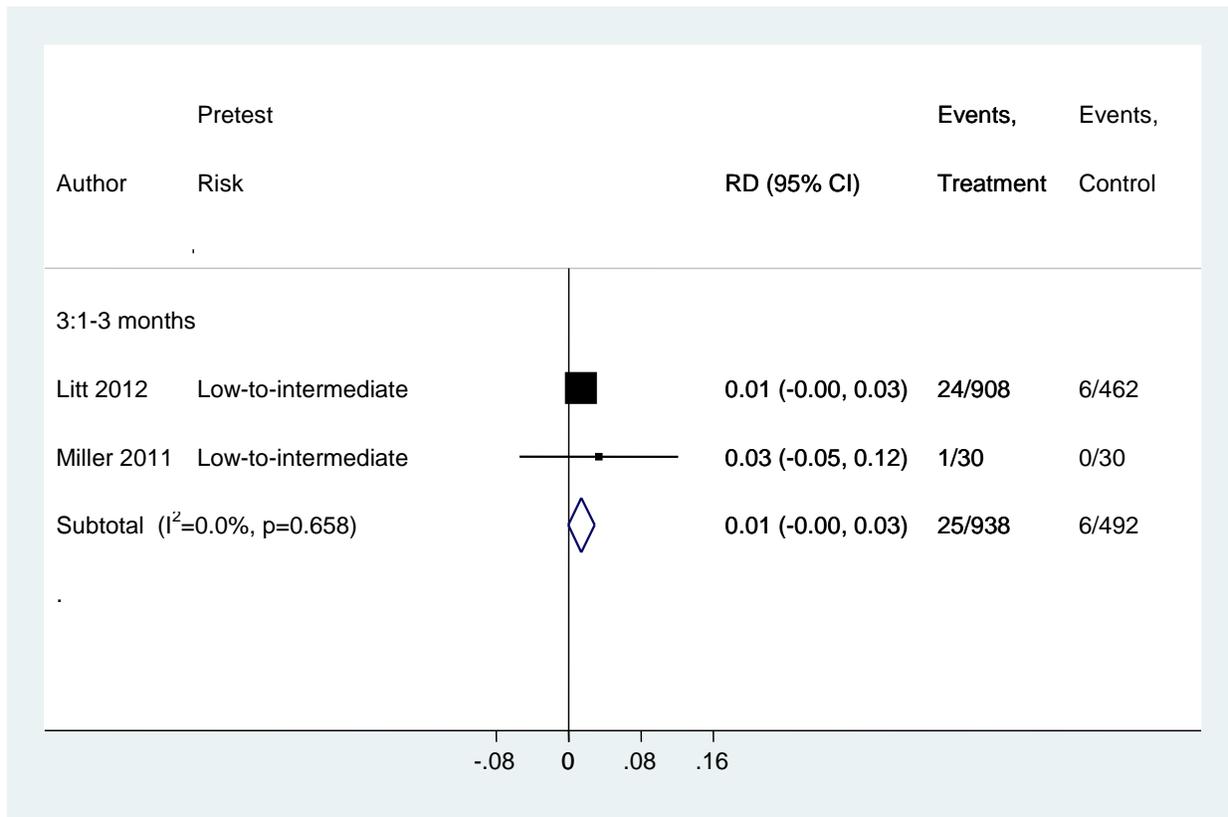
during the 30- and 90-day followup periods as reported by both trials (pooled, 5.2% vs. 4.7%, RD 1, 95% CI -1 to 3 per 100 people, $I^2=0\%$) (Figure 10).^{77, 79} However, ICA results showed fewer false positives (i.e., no obstructive CAD) in patients referred following CCTA compared with usual testing: at the index ED visit (24% vs. 56%) and at 30 days (29% vs. 53%) in the larger trial,⁷⁷ and during 90 days of followup (25% vs. 75%) in the smaller trial.⁷⁹ The larger trial found that CCTA testing was associated with less stress testing than usual care at the index ED visit (13.7% vs. 57.8%, RD -44.1, 95% CI -49.2 to -39.1 per 100) and less additional noninvasive testing of any type within 30 days in the CCTA group (23.1% vs. 66.4%, RD -43.3, 95% CI -48.4 to -38.1 per 100 people). While stress testing through 30 days of followup was done in fewer CCTA patients (16.9% vs. 59.8%, RD -42.9, 95% CI -48.0 to -37.8 per 100), a similar number of patients in the CCTA and usual care groups received resting echocardiogram within 30 days (6.2% vs. 6.6%).⁷⁷ The smaller trial of 60 patients found that through 90 days of followup, the CCTA group had less additional noninvasive testing (33% vs. 60%, RD -27, 95% CI -51 to -2), which included exercise stress testing (7% vs. 20%), nuclear perfusion testing (10% vs. 20%), transthoracic echocardiography (7% vs. 17%), and stress echocardiography (10% vs. 3%).⁷⁹ CCTA was associated with slightly more revascularization procedures at the time of the index visit as reported by the larger trial (2.5% vs. 0.9%, RD 1.7, 95% CI 0.3 to 3.0 per 100 people),⁷⁷ while revascularization was similar between the CCTA and usual care groups during the 30- and 90-day followup periods as reported across both trials (pooled, 2.7% vs. 1.2%, RD 1, 95% CI 0 to 3 per 100 people, $I^2=0\%$) (Figure 11).^{77, 79} There were no significant differences between the CCTA group and the usual care group in prescription or use of medications (aspirin, thienopyridines, or statins) at either the index visit or during 30 days of followup in the larger trial.⁷⁷ There were also no differences between the two groups in the likelihood of having a followup visit with a cardiologist^{77, 79} or with a primary care or other physician.⁷⁹

Figure 10. Meta-analysis results for risk of invasive coronary angiography across studies comparing CCTA with usual care in patients with low to intermediate pretest risk



CCTA = coronary computed tomography angiography; CI = confidence interval; RD = risk difference.

Figure 11. Meta-analysis results for risk of revascularization across studies comparing CCTA with usual care in patients with low to intermediate pretest risk



CCTA = coronary computed tomography angiography; CI = confidence interval; RD = risk difference.

Harms of index test and consequences of testing. The larger trial reported a similarly low incidence of bradycardia (presumed to be related to the medication to control heart rate) following CCTA (0.1%) and usual care (0.2%).⁷⁷

Harms of additional testing, differential effectiveness or safety in subgroups. Not reported for low to intermediate risk patients.

Anatomic Tests Versus Functional Tests

CCTA Versus Exercise ECG

Two fair-quality studies, including one trial and one retrospective observational study, compared 64-slice dual source CCTA with exercise ECG in patients at low to intermediate pretest risk (Appendix E, Tables E28–E35, E40, G3).^{75, 94} Exercise ECG followed the Bruce protocol in the trial and a “standardized protocol” in the observational study. Patients enrolled in the RCT (N=562) presented to a single emergency department in Australia with acute, undifferentiated chest pain.⁷⁵ This trial was supported by various grants (Queensland Emergency Medicine Research Foundation, Smart Future Fellowship Early Career Grant, and the Washington–Queensland Trans-Pacific Fellowship fund). In the observational study (N=498), patients with stable angina were referred from primary care to one of two clinics in Denmark based on geographic location, with one clinic using CCTA and the other exercise ECG as the

primary initial test for CAD.⁹⁴ The source of funding was not reported for this study. Within each study, patients in the CCTA and exercise ECG groups were similar in age, sex, and cardiac risk factors. Across the trial and the observational study, mean ages (52 vs. 55 years) and sex (female 42% vs. 48%) were similar, respectively; however, the two populations differed regarding symptoms and various cardiac risk factors, respectively, including typical angina (90% vs. 14%), hypertension (31% vs. 56%), hyperlipidemia (25% vs. 83%), and smoking (23% vs. 48%). In the observational study, the mean overall baseline risk score (according to Diamond and Forrester) was 26 ± 23 percent and did not differ between test groups; the trial did not report baseline risk scores for its population. Both studies reported outcomes at 12 months, and the trial also reported outcomes at 1 and 6 months. Methodological shortcomings included unclear randomization sequence generation and allocation concealment in the RCT and unclear blinding of outcomes assessment in both studies.

Clinical outcomes. In the trial of ED patients, there were no deaths through 30 days and similar mortality rates between CCTA and exercise ECG groups through 12 months (0.6% vs. 0.4%, RD 0.2, 95% CI -1.0 to 1.4 per 100 people).⁷⁵ None of the deaths were cardiac-related. At the index visit, MI diagnosis occurred similarly in CCTA and exercise ECG groups (1.9% vs. 1.7%, RD 0.2, 95% CI -2.0 to 2.4 per 100) and there were no additional MIs through 30 days in either group.⁷⁵ Unstable angina was similar between groups at the index visit (3.4% vs. 1.3%, RD 2.2, 95% CI -0.3 to 4.6 per 100) and no additional cases were reported through 30 days. Through 12 months followup, hospitalizations for any reason (10.2% vs. 10.8%) and ED visits for recurrent chest pain or cardiac symptoms (12.5% vs. 10.5%) were similar between groups. However, the length of stay in the ED was significantly shorter in the CCTA group compared with the exercise ECG group (13.5 vs. 19.7 hours; $p=0.003$). Outcomes in the observational study of outpatients were similar, with no deaths through 12 months, and no difference in the risk of MI between CCTA and exercise ECG groups (0% vs. 1.2%, unadjusted $p=0.08$) through the same followup period.⁹⁴

Clinical management. While the trial found that CCTA was associated with more ICA referrals through 12 months (9.0% vs. 2.3%, RD 4.8, 95% CI 0.8 to 8.9 per 100), the observational study reported the opposite, although the results did not reach statistical significance (17.5% vs. 22.7%; unadjusted RR 0.7, 95% CI 0.54 to 1.1). Through 12 months, CCTA was associated with significantly more people undergoing revascularization compared with exercise ECG (4.3% vs. 1.3%, RD 3.1, 95% CI 0.5 to 5.7 per 100)⁷⁵ in the RCT. In terms of the patients who tested positive after CCTA ($n=31$) and exercise ECG ($n=65$), the observational study found that CCTA patients were more likely to undergo revascularization through 12 months (45% vs. 17%, unadjusted RR 2.7, 95% CI 1.4 to 5.2), including PCI (29% vs. 15%, unadjusted RR 1.9, 95% CI 0.9 to 4.2, $p=NS$) and CABG (16% vs. 2%, unadjusted RR 11, 95% CI 1 to 86).⁹⁴ Additional noninvasive testing was done in significantly fewer CCTA patients in the observational study (4.8% vs. 13.4%, unadjusted RR 0.4, 95% CI 0.2 to 0.7).⁹⁴

Harms of index test and consequences of testing. The mean radiation exposure with index CCTA was reported by both studies: 3.8 mSv (95% CI 3.5, 4.1 mSv) in the trial⁷⁵ and 7.5 ± 3.6 mSv in the observational study.⁹⁴

Harm of additional testing. Radiation dose was also reported for index testing plus downstream diagnostic tests in a fair-quality retrospective cohort, with the CCTA group having significantly greater exposure compared with exercise ECG regardless of initial test result (range of means for positive, negative, and inconclusive test results: 7.8 to 13 vs. 0.7 to 5.4, $p<0.001$ for

all comparisons), but not when downstream revascularization was considered in test positive patients (28 [CCTA] versus 32 [exercise ECG], $p=0.61$) (Appendix G, Table G4).

Differential effectiveness or safety in subgroups: No analyses related to differential effectiveness or safety of CCTA versus exercise ECG with regard to patient characteristics or other factors were provided in either study

CCTA Versus SPECT

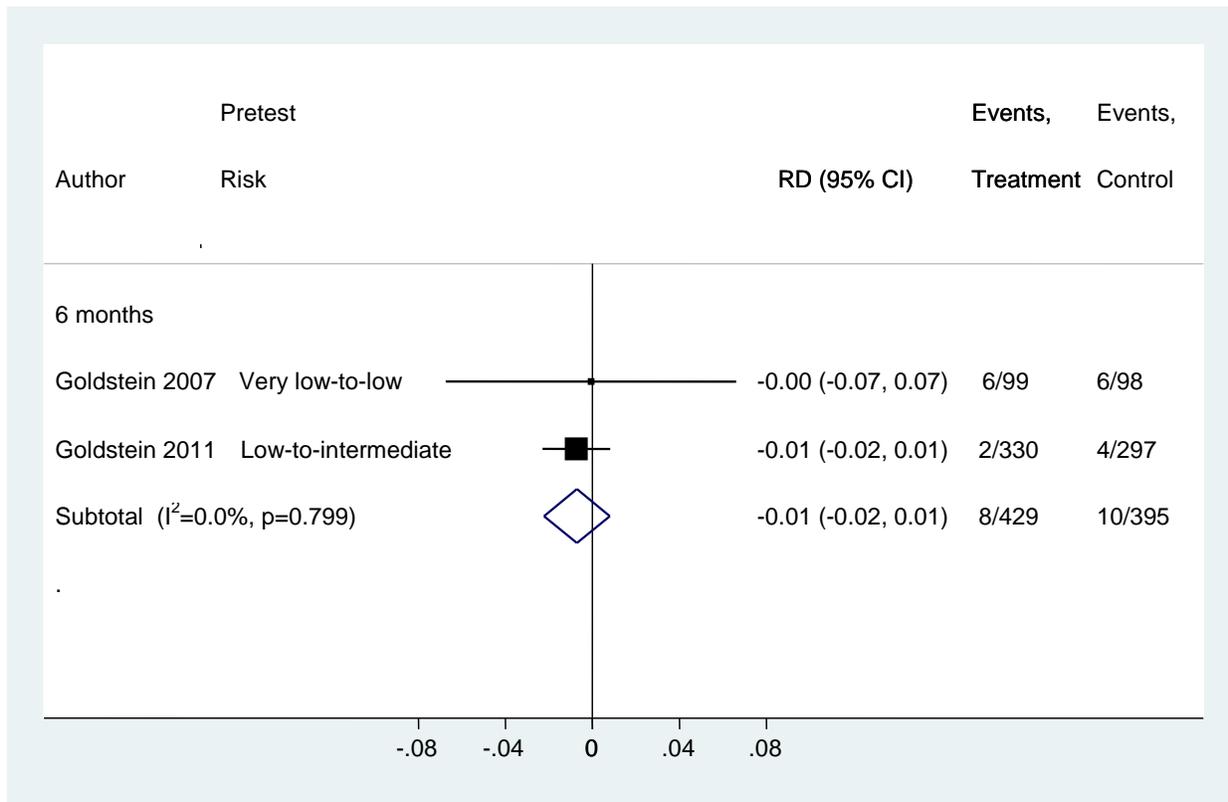
Two trials, one good-quality⁷³ and one fair-quality⁷⁴ and one fair-quality observational study⁸⁴ compared CCTA with SPECT in patients with low to intermediate risk (Appendix E, Tables E28–E35, E40, G3).

Goldstein et al. conducted two trials of patients presenting to the ED with acute chest pain; one trial published in 2007 enrolled 203 patients⁷⁴ and the other, published in 2011, enrolled 749 patients⁷³ (the enrollment periods do not overlap). Although Goldstein et al. 2007 specified patients be at very low to low pretest risk and Goldstein et al. 2011 included patients at low to intermediate pretest risk, the median TIMI scores were identical in both studies (1.0). Because of this, and because demographics and outcomes were similar across both studies, they are analyzed here together as trials of low to intermediate risk patients. The 2007 trial collected data from a single ED,⁷⁴ while the 2011 trial was multicenter (16 EDs).⁷³ Both trials were conducted in the United States and received funding via research grants from the Minestrelli Advanced Cardiac Research Imaging⁷⁴ and Bayer Pharmaceuticals.⁷³ CCTA scans were obtained with a 64-slice CT in the earlier trial or a 64 to 320-slice CT scanner in the other. The 2007 trial employed exercise stress SPECT while the 2011 trial used either exercise or pharmacological stress though the percentage of patients who received each type of stress was not reported. No patients had a history known CAD. Aside from the 2007 trial having slightly younger (mean age 48 vs. 51 years) and fewer male patients (43% vs. 57%) in the CCTA group than the SPECT group, the trials had similar baseline characteristics and cardiac risk factors (i.e., hypertension, dyslipidemia, diabetes, smoking) between groups. Mean age was 50 years in both trials, and males comprised 49.5 percent (2007) and 46.1 percent (2011) of patients. The 2007 trial had considerably more patients with a family history of CAD (41.6%) than did the 2007 study (30.3%). Outcomes were reported through 6 months, with complete followup of 97.0 and 89.7 percent, respectively. The 2011 trial had no apparent methodological shortcomings.⁷³ However, the 2007 trial had several methodological shortcomings including unclear methods for allocation concealment, lack of analysis according to allocated treatment assignment, lack of blinded outcomes assessment and significant baseline differences between groups that were not controlled for.⁷⁴

Cheezum et al. retrospectively enrolled 252 consecutive patients who had undergone exercise stress (72%) or pharmacologic stress (28%) SPECT who were then matched by age and sex to 241 patients who underwent 64-slice CCTA. All patients were at intermediate risk presenting with chest pain (89%) or dyspnea (11%) to a single center in the United States (90.0% were outpatients).⁸⁴ According to Diamond-Forrester, the overall pretest risk was very low (<5%) in 3 percent, low (5%–10%) in 14.5 percent, and intermediate (10%–90%) in 82.5 percent of the population. No patient had a history of CAD. The majority of patient characteristics were similar between groups; the mean age was 53 years, and 44.5% of patients were female. Patients were followed for a mean of 30 ± 7 months, with complete followup in 97.2% of patients. The only methodological shortcoming was lack of blinded outcomes assessment.

Clinical outcomes. No patients died through 6 months followup in either trial. The 2007 trial reported no MI events in either group at any time through 6 months.⁷⁴ In contrast, the 2011 trial reported a total of six MI events at the index visit; although the cause and precise timing of these events was not reported, they were not detected by resting ECG or serum biomarker testing within the first 4 hours of evaluation (otherwise the patients would have been excluded) and thus occurred or were detected after study enrollment. CCTA and SPECT patients had a similar risk of MI diagnosis at the index ED visit (0.3% vs. 1.5%, RD -1.2%, 95% CI -2.6% to 0.19%); no additional MI events occurred in either group after the index visit through 6 months followup.⁷³ The 2011 trial reported no repeat cardiovascular hospitalizations in either group through 6 months.⁷³ Both trials reported a similar occurrence of repeat ED visits for cardiovascular causes between the CCTA and SPECT groups through 6 months (1.9 vs. 2.5 per 100 people; pooled RD -1, 95% CI -2 to 1) (Figure 12); these visits occurred in fewer patients in the 2011 trial (0.6% vs. 1.3%, RD -0.7, 95% CI -2.3% to 0.8%)⁷³ than in the 2007 trial (6% in both groups).⁷⁴ Repeat cardiovascular office visits occurred in 2 percent of patients in both groups in the 2007 trial. Test results were normal in fewer CCTA patients than SPECT patients in both the 2011 trial (82.2% vs. 89.9%, RD -7.7%, 95% CI -12.8% to -2.6%) and in the 2007 trial (68% vs. 95%, RD -27%, 95% CI -37% to -17%). The 2007 trial reported that the diagnosis was “clinically correct” in a similar percentage of patients between groups (95% vs. 91%, RD 4%, 95% CI -3% to 11%) according to either a definitive diagnosis made during ICA or by the occurrence of MACE including cardiac death, acute MI, or unstable angina through 6 months followup.⁷⁴ Clinical outcomes for test-positive versus test-negative patients were not reported by either trial.

Figure 12. Meta-analysis results for risk of repeat cardiovascular emergency department visits across studies comparing CCTA with SPECT in patients with low to intermediate pretest risk



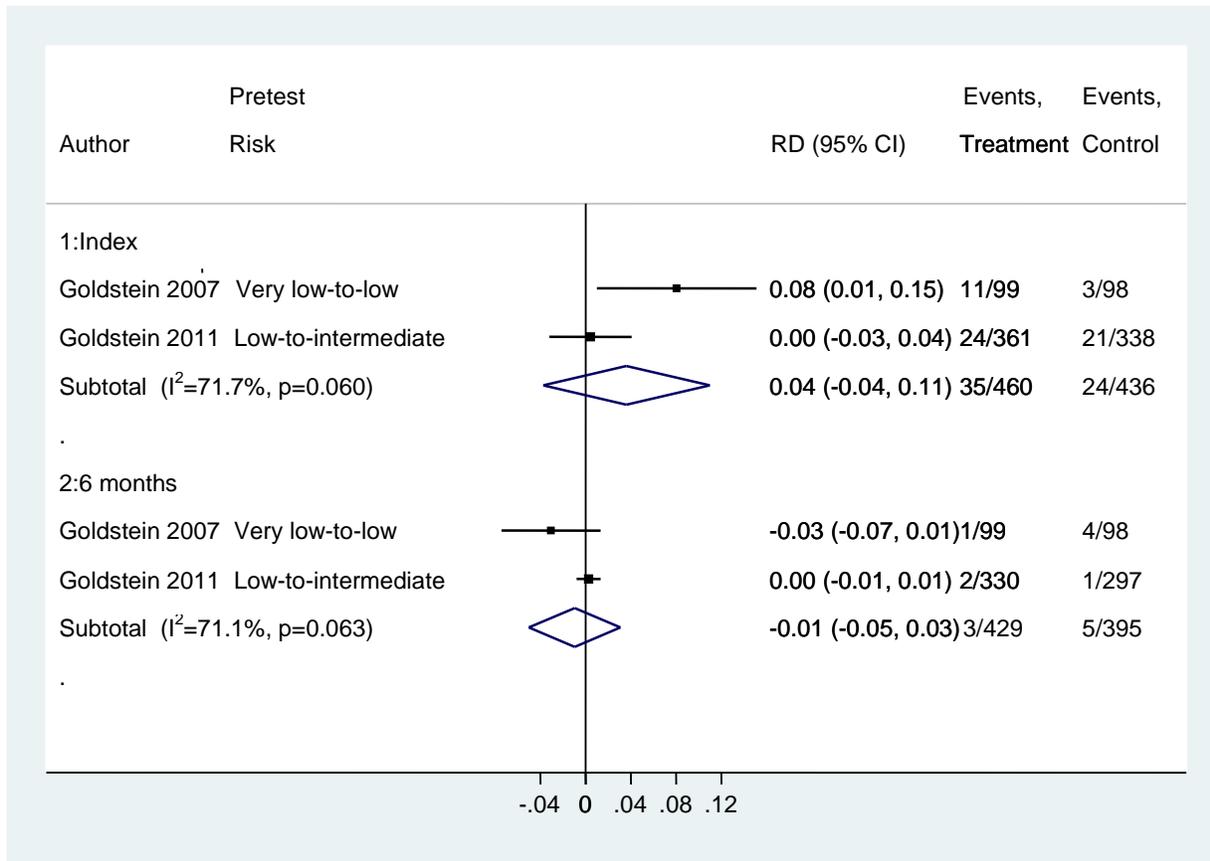
CCTA = coronary computed tomography angiography; CI = confidence interval; RD = risk difference; SPECT = single positron emission tomography.

The observational study reported all events through a mean of 30 ± 7 months.⁸⁴ There were no cardiovascular deaths in either group; 2.4 percent of patients in both groups died of other unknown causes through the followup period as identified upon medical record review. The risk of the composite MACE outcome (cardiac death, MI, acute coronary syndrome, or revascularization) was similar between CCTA and SPECT patients (0.4% vs. 0.9%). Cardiovascular hospitalization occurred similarly in the CCTA and SPECT groups (6.6% vs. 4.3%) as did cardiovascular ED visits (13.1% vs. 14.0%). Clinical outcomes were not stratified by test results.⁸⁴

Clinical management. ICA referral rates were similar between CCTA and SPECT groups in both trials at the index visit (7.6% vs. 5.5%, pooled RD 4, 95% CI -4 to 11 per 100 people, I²=71.7%) as well as through 6 months (0.7% vs. 1.3%, pooled RD -1, 95% CI -5 to 3 per 100, I²=71.1%) (Figure 13).^{73, 74} In the smaller trial, of those referred for ICA the results showed a similar proportion of false positives (i.e., no obstructive CAD) between groups (CCTA 25% vs. SPECT 29%, respectively).⁷⁴ At the index ED visit, 10.7 percent (2011 trial) and 24 percent (2007 trial) of patients in the CCTA group underwent additional testing with SPECT, while 1.8% (2011 trials) of patients in the SPECT group underwent additional testing with CCTA at this initial visit. Overall, additional noninvasive testing at the index visit occurred more commonly in the CCTA group, with the larger trial reporting 10.2% for CCTA and 0.9% for SPECT (RD 9.4, 95% CI 6.1 to 12.7 per 100 patients) and the smaller trial reporting 24% for CCTA and 0% for

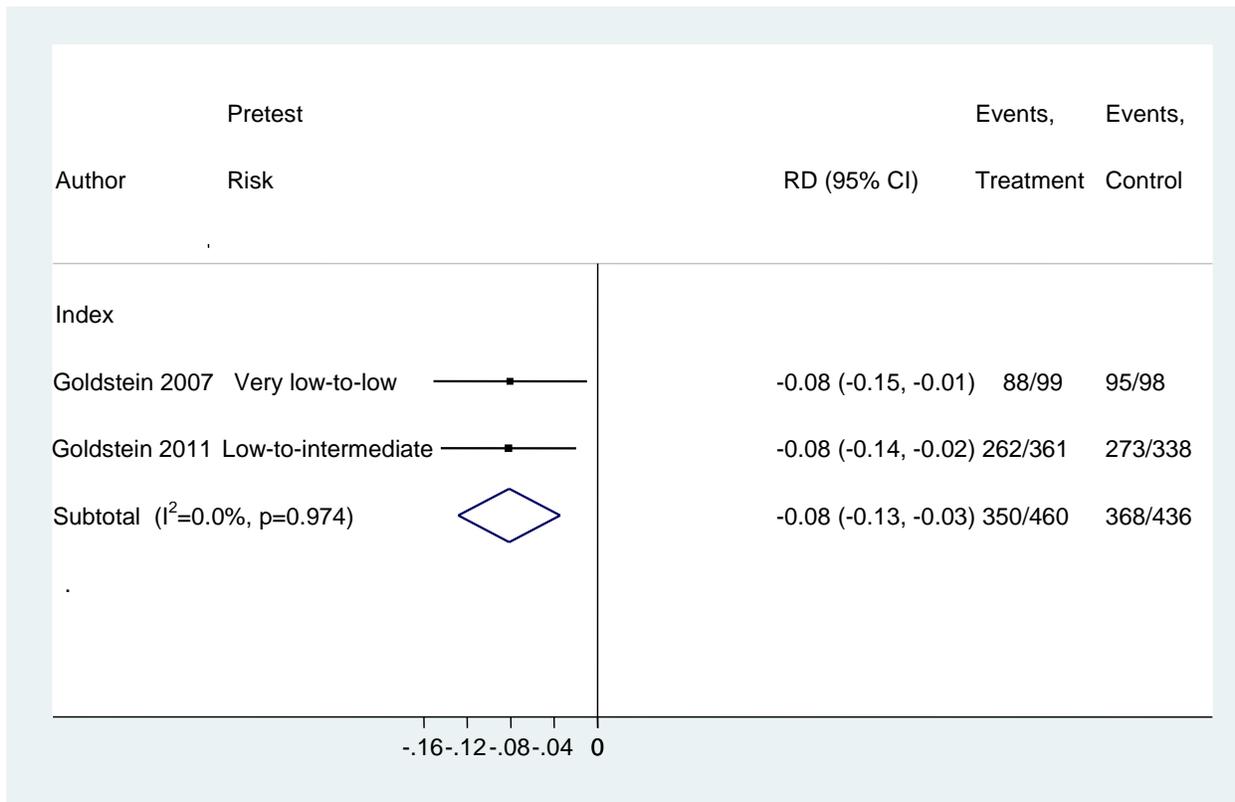
SPECT (RD 24 per 100 people, $p < 0.001$). The smaller trial found that after the index visit through 6 months followup, additional SPECT was done similarly across both groups (1% vs. 3%).⁷⁴ Across both studies, fewer CCTA patients were discharged home from the ED at the index visit (76.1% vs. 84.4%, pooled RD -8, 95% CI -13 to -3 per 100 patients, $I^2 = 0\%$) (Figure 14); in general, discharge occurred upon normal test results.^{73, 74} Across both trials, CCTA and SPECT groups were similar regarding revascularization at the index ED visit (3.9% vs. 2.1%, pooled RD 2, 95% CI 0 to 4 per 100 people, $I^2 = 3.8\%$) and after the index visit through 6 months (0.5% vs. 0%, pooled RD 0, 95% CI 0 to 1 per 100, $I^2 = 3.8\%$) (Figure 15); this effect was consistent for both PCI and CABG evaluated separately at the index ED visit (PCI: 2.5% to 3% vs. 1.0% to 2.4%; CABG: 1.1% to 2.0% vs. 0%) and through 6 months (PCI: 0.3% to 1.0% vs. 0%; CABG: 0% in both groups).^{73, 74}

Figure 13. Meta-analysis results for risk of referral for invasive coronary angiography across studies comparing CCTA with SPECT in patients with low to intermediate pretest risk



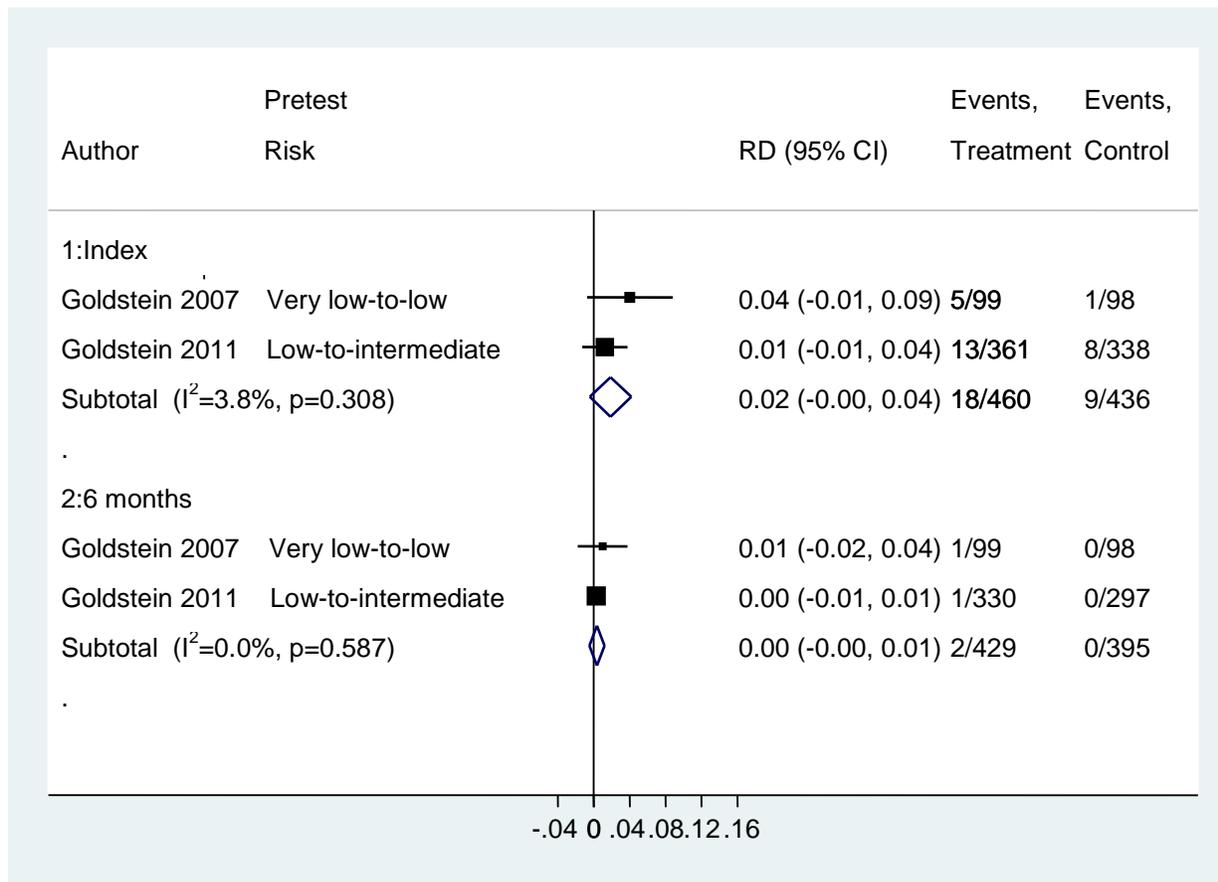
CCTA = coronary computed tomography angiography; CI = confidence interval; RD = risk difference; SPECT = single positron emission tomography.

Figure 14. Meta-analysis results for discharge to home following index visit across studies comparing CCTA with SPECT in patients with low to intermediate pretest risk



CCTA = coronary computed tomography angiography; CI = confidence interval; RD = risk difference; SPECT = single positron emission tomography.

Figure 15. Meta-analysis results for risk of revascularization across studies comparing CCTA with SPECT in patients with low to intermediate pretest risk



CCTA = coronary computed tomography angiography; CI = confidence interval; RD = risk difference; SPECT = single positron emission tomography.

The observational study reported all events through a mean of 30 ± 7 months.⁸⁴ CCTA patients were less likely than SPECT patients to undergo ICA (3.3% vs. 8.1%, RR 0.4, 95% CI 0.2 to 0.9) or additional testing with CCTA (0.4% vs. 4.7%, RR 0.1, 95% CI 0.01 to 0.7). Also, of those patients referred for ICA, there were fewer false positives (i.e., no obstructive CAD) after CCTA versus SPECT (33% vs. 60%). However, the groups were similar in regards to other types of noninvasive test utilization, including SPECT (5.7% vs. 6.0%), exercise echocardiography (1.2% vs. 0.9%), and exercise ECG (2.5% vs. 2.1%). Overall, CCTA patients were slightly less likely to need additional testing than SPECT patients although this difference did not reach statistical significance (11.5% vs. 17.0%, RR 0.7, 95% CI 0.4 to 1.1).⁸⁴

Harms of index test and consequences of testing. There were no test complications in either group as reported by the 2007 Goldstein trial.⁷⁴ The 2011 Goldstein trial noted that radiation exposure at the index visit was significantly lower in the CCTA group compared with the SPECT group (median 11.5 vs. 12.8 mSv, $p=0.02$).⁷³ In the observational study, incidental findings requiring further investigation following CCTA occurred in 7.1% of patients. In the 252 patients who received CCTA, pulmonary nodule (≥ 4 mm) was found in five patients; hepatic cyst in three patients; liver hemangioma, fatty liver, and mediastinal lymphadenopathy in two

patients each; pulmonary embolism, thoracic aortic aneurysm, esophageal thickening, and pleural thickening in one patient each.

Harms of additional testing. No harms of additional testing were reported in any of the three studies.

Harms of additional testing differential effectiveness or safety in subgroups. Not reported for this patient population.

Noncomparative Studies: Anatomical

Calcium scoring. Three noncomparative studies of calcium scoring in patients at low to intermediate pretest risk reported on predictive accuracy. One study was conducted in an outpatient setting (N=422),¹⁰³ one in the emergency department (ED) (N=263),¹¹⁴ and the setting was unclear in the third study which was in patients who were referred for invasive coronary angiography (N=2088).¹¹² Of note, this latter study excluded patients who underwent elective revascularization within 60 days after index CT to control for procedure-driven events. Patients presenting to the emergency department were younger, more likely male, and, with the exception of smoking which was higher in this population, had fewer cardiac risk factors than patients in the other studies. Mean ages ranged from 47.3 to 58.6 years across studies and a slight majority of patients were male (49.3%–60%). In terms of test-positive patients, in all studies, the frequency of cardiac events was higher compared with test-negative patients. Across the two non-ED studies with mean followups of 2.5 years, the frequency of any cardiac event was 5 and 11 per 100 people (vs. 1 per 100 people in both), mortality was 2 per 100 people in both (vs. 0 and 1 per 100 people), and MI was 1 and 2 per 100 people (vs. 0 events); in the ED study, over 5 years followup, the frequency of any cardiac event was 20 per 100 people compared with no events (Appendix F, Tables F7–F10).

Noncomparative Studies: Functional

Stress echocardiography. Two noncomparative studies of stress echocardiography in patients at low to intermediate pretest risk reported on predictive accuracy. One study was conducted in an outpatient setting and used treadmill exercise only (N=7236)¹⁰⁶ while the other was conducted in an emergency department and employed exercise (72%) or dobutamine (28%) as a stressor (N=108).¹⁰² The mean age of both study populations was 54 ± 12 years. Compared with the ED study, the outpatient study enrolled fewer females (30% vs. 50%), had more patients with hyperlipidemia (59% vs. 31%) and included patients with known CAD (10% vs. 0%). In terms of test-positive patients, regardless of setting, the frequency of cardiac events was greater compared with test-negative patients. In the outpatient setting, over a mean followup of 4.8 years of followup, higher annualized mortality rates per person year of followup were reported: ischemia (0.53, 95% CI 0.33 to 0.80) and fixed wall motion abnormality (0.93, 95% CI 0.56 to 1.31) versus normal (0.30, 95% CI 0.24 to 0.37). In the emergency room setting, the frequency of any cardiac event over a mean followup period of 1 year was 75 per 100 people compared with no events (Appendix F, Tables F5–F8).

Stress ECG. Four noncomparative studies of stress ECG in patients at low to intermediate pretest risk reported on predictive accuracy. Three studies employed exercise stress (treadmill or bicycle)^{101, 103, 108} and one used either exercise or dobutamine stress.¹⁰² One study was conducted in an outpatient setting, one in an emergency department, and the setting was unclear in the remaining two studies. Samples sizes ranged from 108 to 2977, mean ages ranged from 50 to 61 years, and the majority of populations were male (51%–60%). The proportion of patients with

relevant cardiac risk factors varied across the studies. As compared with a negative result, a positive stress ECG was associated with a higher frequency of any cardiac event across three of the studies (N=5353) with followup ranging from 1 to 3 years (2 to 30 per 100 people vs. 1 to 3 per 100 people). Of note the largest event rate (30%) in those who tested positive was seen in the study conducted in the emergency room at 1 year of followup. In the fourth study (N=422),¹⁰³ the frequency of cardiac events over a mean 2.6 years was similar between groups (5 and 4 per 100 people) as was mortality (0 for both) and myocardial infarction (1 per 100 people for both) (Appendix F, Tables F7–F8).

Table 9. Summary of findings and strength of evidence: Low to intermediate pretest risk

Outcome*	Comparison	Number of Studies (N)	Setting	Conclusions	Strength of Evidence
Mortality (all-cause)	CCTA vs. Usual Care [†]	1 RCT (N=1392)	ED	There is low strength of evidence that a difference in mortality was not found. No deaths occurred in either group through 1 month.	Low
	CCTA vs. Exercise ECG	1 RCT (N=562) 1 observational (N=498)	ED (RCT) Outpatient (observational)	There is low strength of evidence that a difference in mortality was not found. No deaths through 1 month. Through 12 months, no difference between groups in mortality (0.6% vs. 0.4%, RD 0.2, 95% CI -1.0 to 1.4 per 100 people) were reported; the observational study reported no deaths.	Low
	CCTA vs. SPECT	2 RCTs (N=952) 1 observational (N=252)	ED (RCTs) Inpatient or outpatient (observational)	There is low strength of evidence that a difference in mortality was not found. No deaths through 6 months (2 RCTs) or through a mean of 30 months (observational study).	Low
Myocardial Infarction	CCTA vs. Usual Care [†]	1 RCT (N=1392)	ED	A difference in diagnosis of MI was not found at the ED index visit (1.0% vs. 0.9% or through 1 month (1.1% in both groups).	Low
	CCTA vs. Exercise ECG	1 RCT (N=562) 1 observational (N=498)	ED (RCT) Outpatient (observational)	A difference in diagnosis of MI was not found at index visit (1.9% vs. 1.7%, RD 0.2, 95% CI -2.0 to 2.4 per 100) and there were no additional MIs through 1 month. Through 12 months, MI occurred similarly between groups (0% vs. 1.2%, p=0.08) based on the observational study.	Low
	CCTA vs. SPECT	2 RCTs (N=952)	ED	No difference in MI diagnosis was found between groups at the index visit (0.3% vs. 1.5%, RD -1.2%, 95% CI -2.6% to 0.19%) (1 RCT, N=749) or through 6 months (0% in both groups) (both RCTs).	Low
Invasive Coronary Angiography referral	CCTA vs. Usual Care [†]	2 RCTs (N=1452)	ED	Referral for ICA was similar between groups at the time of index ED visit (1 RCT, N=1392) (4.1% vs. 3.9%) and through 1- to 3-months (2 RCTs) (pooled 5.2% vs. 4.7%, RD 1, 95% CI -1 to 3 per 100).	Low

Outcome*	Comparison	Number of Studies (N)	Setting	Conclusions	Strength of Evidence
	CCTA vs. Exercise ECG	1 RCT (N=562)	ED	CCTA associated with more ICA referrals through 12 months (9.0% vs. 2.3%, RD 4.8, 95% CI 0.8 to 8.9 per 100).	Low
	CCTA vs. Exercise ECG	1 observational (N=498)	Outpatient	There were fewer ICA referrals in the CCTA group through 12 months (17.5% vs. 22.7%; unadjusted RR 0.7, 95% CI 0.54 to 1.1, p=NS). Definitive conclusions are not possible [‡]	Insufficient
	CCTA vs. SPECT	2 RCTs (N=952)	ED	ICA referral rates were similar at the index ED visit (7.6% vs. 5.5%, pooled RD 4, 95% CI -4 to 11 per 100, I ² =71.7%) and through 6 months (0.7% vs. 1.3%, pooled RD -1, 95% CI -5 to 3 per 100, I ² =71.1%).	Low
	CCTA vs. SPECT	1 observational (N=252)	Inpatient or outpatient	CCTA patients were less likely than SPECT patients to undergo ICA (3.3% vs. 8.1%, RR 0.4, 95% CI 0.2 to 0.9) through a mean of 30 months. Definitive conclusions are not possible [‡]	Insufficient
Revascularization	CCTA vs. Usual Care [†]	2 RCTs (N=1452)	ED	At the index visit, CCTA was associated with slightly more revascularization procedures (2.5% vs. 0.9%, RD 1.7, 95% CI 0.3 to 3.0 per 100) in one trial (N=1392). During 1- to 3-month followup, revascularization was similar between CCTA and usual care groups (pooled, 2.7% vs. 1.2%, RD 1, 95% CI 0 to 3 per 100 people) based on both trials.	Low
	CCTA vs. Exercise ECG	1 RCT (N=562)	ED	Revascularization was significantly more common in CCTA versus exercise ECG through 12 months (4.3% vs. 1.3%, RD 3.1, 95% CI 0.5 to 5.7 per 100).	Low
	CCTA vs. Exercise ECG	1 observational (n=96 subset of test-positive patients)	Outpatient	Revascularization was more common following positive CCTA than positive exercise ECG through 12 months (45% vs. 17%, unadjusted RR 2.7, 95% CI 1.4 to 5.2). Definitive conclusions are not possible [‡]	Insufficient
	CCTA vs. SPECT	2 RCTs (N=952)	ED	Revascularization at the ED index visit (3.9% vs. 2.1%, pooled RD 2 per 100, 95% CI 0 to 4) and after this visit through 6 months (0.5% vs. 0%, pooled RD 0, 95% CI 0 to 1 per 100) was similar between groups.	Moderate
Percutaneous Coronary Intervention	CCTA vs. Usual Care [†]	1 RCT (N=60)	ED	Similarly low rates between groups over 3 months followup (CCTA 3% vs. usual care 0%); unclear if this estimate includes the index visit.	Low

Outcome*	Comparison	Number of Studies (N)	Setting	Conclusions	Strength of Evidence
	CCTA vs. SPECT	2 RCTs (N=952)	ED	Across both trials, PCI use was similar at the index visit 2.5% to 3% versus 1.0% to 2.4%, RD 0.13 to 2.0 per 100, p=NS) and through 6 months (0.3% to 1.0% vs. 0%, RD 0.3 to 1.0 per 100, p=NS).	Moderate
	CCTA vs. Exercise ECG	1 observational (n=96 subset of test-positive patients)	Outpatient	More patients who tested positive with CCTA underwent PCI through 12 months compared with those who tested positive with exercise ECG (29% vs. 15%, unadjusted RR 1.9, 95% CI 0.9 to 4.2, p=NS). Definitive conclusions are not possible [‡]	Insufficient
Coronary Artery Bypass Graft	CCTA vs. Usual Care [†]	1 RCT (N=60)	ED	A difference in CABG use was not found. No CABG procedures reported in either group through 3 months.	Low
	CCTA vs. SPECT	2 RCTs (N=952)	ED	A difference in referral for CABG was not found at the ED index visit (1.1% to 2.0% vs. 0%) or after this visit through 6 months (0% in both groups).	Moderate
	CCTA vs. Exercise ECG	1 observational (n=96 subset of test-positive patients)	Outpatient	Those who tested positive after CCTA were more likely to undergo CABG through 12 months than those who tested positive with exercise ECG (16% vs. 2%, unadjusted RR 11, 95% CI 1 to 86). Definitive conclusions are not possible [‡]	Insufficient
Additional Testing	CCTA vs. Usual Care [†]	2 RCTs (N=1452)	ED	At the ED index visit, CCTA testing was associated with less stress testing than usual care (13.7% vs. 57.8%, RD -44.1, 95% CI -49.2 to -39.1 per 100) (1 RCT, N=1392). During the followup period, additional noninvasive testing was done in fewer patients in the CCTA group through 1 month (23.1% vs. 66.4%, RD -43.3, 95% CI -48.4 to -38.1 per 100 people) (1 trial, N=1392) and through 3 months (33% vs. 60%, RD -27, 95% CI -51 to -2) (1 trial, N=60).	Moderate (30 days) Low (90 days)
	CCTA vs. Exercise ECG	1 observational (N=498)	Outpatient	Additional noninvasive testing was less common following CCTA than exercise ECG through 12 months (4.8% vs. 13.4%, unadjusted RR 0.4, 95% CI 0.2 to 0.7). Definitive conclusions are not possible [‡]	Insufficient

Outcome*	Comparison	Number of Studies (N)	Setting	Conclusions	Strength of Evidence
	CCTA vs. SPECT	2 RCTs (N=952)	ED	At the index visit, additional noninvasive testing was more commonly done in the CCTA group, with the larger trial reporting 10.2% for CCTA and 0.9% for SPECT (RD 9.4, 95% CI 6.1 to 12.7 per 100 patients) and the smaller trial reporting 24% for CCTA and 0% for SPECT (RD 24 per 100 people, p<0.001). There were no significant differences between groups in additional testing through 6 months as reported by one trial (1% vs. 3%).	High (index visit) Low (6 months)
	CCTA vs. SPECT	1 observational (N=252)	Inpatient or outpatient	A difference was not found for additional testing at a mean of 30 months including SPECT (5.7% vs. 6.0%), exercise echocardiography (1.2% vs. 0.9%), or exercise ECG (2.5% vs. 2.1%). Definitive conclusions are not possible‡	Insufficient
Hospitalization (Cardiac related)	CCTA vs. Usual Care†	2 RCTs (N=1452)	ED	One trial (N=1392) reported that the CCTA group was significantly less likely to be hospitalized or admitted for observation at the ED index visit (50% vs. 77%, RD -26.8, 95% CI -31.9 to -21.8 per 100). During followup, 1-month rates of cardiac hospitalization were similar between groups (3% vs. 2%).	Moderate
	CCTA vs. SPECT	1 RCT (N=749) 1 observational (N=252)	ED (RCT) Inpatient or outpatient (observational)	Frequency of hospitalization was similar between groups The RCT reported no cardiovascular hospitalizations through 6 months and the observational study reported similar results between groups (6.6% vs. 4.3%) through a mean of 30 months.	Moderate
Harms of Index Test	CCTA vs. Usual Care†	1 RCT (N=1392)	ED	A difference in bradyarrhythmia was not found; it occurred in one patient in each group (0.1% vs. 0.2%).	Low
	CCTA vs. SPECT	1 observational (N=252)	Inpatient or outpatient	Incidental findings requiring further investigation occurred following CCTA in 7.1% of patients. Definitive conclusions are not possible‡	Insufficient

CABG = coronary artery bypass graft; CCTA = coronary computed tomography angiography; CI = confidence interval; ED = emergency department; ICA = invasive coronary angiography; PCI = percutaneous coronary intervention; MI = myocardial infarction; NS = not statistically significant; RCT = randomized controlled trial; RD = risk difference; RR = relative risk; SPECT = single photon emission computed tomography.

*Primary outcomes not listed in this table had no evidence and thus insufficient strength of evidence.

†Usual consisted of traditional “rule out” approaches at the discretion of the patients’ treating physician (64% underwent diagnostic testing, primarily stress testing with imaging) in one trial (N=1392) and standard treatment (12-lead ECG, coronary biomarkers, continuous ECG monitoring, medication, cardiology consultation, and additional cardiac testing as required) in the other trial (N=60).

‡Definitive conclusions are not possible due to study limitations and/or imprecision in observational studies.

Intermediate To High Pretest Risk of Coronary Artery Disease

Key Points

Evidence for all primary outcomes and comparators not listed below was insufficient to draw conclusions due to study limitations and/or imprecision in the observational study or due to lack of evidence.

CCTA Versus SPECT

- In intermediate to high risk patients, there is insufficient evidence from one small poor-quality trial with a mean of 1.8 months followup that there were no deaths or MIs found. Strength of evidence was low that cardiac hospitalizations occurred similarly between groups. CCTA was associated with more revascularizations, as well as slightly more ICA referrals and slightly but not significantly less noninvasive cardiac imaging tests through the same followup period (low strength of evidence).

Detailed Synthesis

A total of three studies were identified in populations with intermediate to high pretest risk of CAD and two (3 publications) included the following comparisons: PET versus SPECT (1 prospective observational)^{87, 89} and CCTA versus SPECT (1 RCT)⁸⁰ (Table 10); one additional noncomparative study reported on the predictive accuracy of stress echocardiography.¹⁰⁴

Functional Tests Versus Functional Tests

PET Versus SPECT

One large, fair-quality, registry-based observational study with two publications compared PET with SPECT (Appendix E, Tables E16–E17)^{87, 89}; no other studies compared different types of functional testing in this population. The study enrolled 1,113 patients at intermediate to high pretest risk presenting with chest pain and/or dyspnea to hospitals and outpatient centers (42 sites) in the United States and Canada.^{87, 89} The study was funded by grants from the National Heart, Lung, and Blood Institute and Bracco Diagnostics. Exercise stress testing was used alone (65%) or in combination with pharmacological stress (7%) in those undergoing SPECT; all patients evaluated with PET had pharmacological stress testing. Those receiving PET were slightly older (mean age 63 vs. 60 years), more likely to be female (59% vs. 51%) and Caucasian (80% vs. 68%) with a greater prevalence of diabetes (41% vs. 31%), elevated cholesterol (65% vs. 60%), and hypertension (73% vs. 66%) compared with those who had SPECT. Angina (68% vs. 79%) was less common in those receiving PET and pretest CAD risk was slightly lower (probability of significant CAD 0.45 vs. 0.38 for SPECT) based on the Pryor method.⁸⁷ Outcomes were reported through both 3 months⁸⁷ and 24 months.⁸⁹ Methodological shortcomings included lack of blinded outcomes assessment and significant baseline differences between groups.

Clinical outcomes. Mortality through 24 months occurred in significantly more PET patients than in those tested with SPECT (5.5% vs. 1.6%, unadjusted RR 3.4, 95% CI 1.6 to 7.2), while MI occurrence was similar between groups (1.1% vs. 1.2%) through the same followup period.⁸⁹ Clinical outcomes for test-positive versus test-negative patients were not reported.

Clinical management. ICA referral rates were higher following PET compared with SPECT at both 90 days (11% vs. 4%, adjusted OR 5.03, 95% CI 1.04 to 24.43) and 24 months (15.0% vs. 6.7%, unadjusted RR 2.2, 95% CI 1.5 to 3.2, $p < 0.0001$); however, there were fewer patients with false positives (i.e., no obstructive CAD) according to ICA results following PET (32.8% vs. 45.8%).⁸⁹ The proportions of those who did not have obstructive disease at ICA who had a positive imaging study were 28.3 percent and 39.1 percent for PET and SPECT⁸⁷; differences did not reach statistical significance (no p-value reported). Overall, more PET patients received revascularization through both 90 days (7% vs. 1.4%, RR 3.5, 95% CI 1.7 to 7.0) and 24 months (8% vs. 2.4%, RR 3.3, 95% CI 1.8 to 6.1). PCI was performed more frequently following PET through 90 days (4.6% vs. 1.4%, RR 3.2, 95% CI 1.5 to 7.1, $p = 0.0020$) and 24 months (5.7% vs. 1.8%, RR 2.9, 95% CI 1.5 to 5.7, $p = 0.0012$); similarly, PET was associated with slightly more CABG procedures than SPECT at the index visit (1.6% vs. 0.4%, RR, 4.6, 95% CI 1.007 to 21.4, $p = 0.0299$) and through 24 months (2.0% vs. 0.4%, RR 5.7, 95% CI 1.3 to 25.5, $p = 0.0103$). Of those who had ICA ($n = 120$), PCI frequency was similar for PET (30%) and SPECT (29%) but CABG was more common following PET versus SPECT (13% vs. 2.6%).⁸⁹ At 90 days, posttest changes in use of aspirin (OR 1.14, 95% CI 0.79 to 1.66), beta-blocker (OR 0.86, 95% CI 0.52 to 1.41), or lipid-lowering agents (OR 1.02, 95% CI 0.71 to 1.47) were similar in both groups after adjustment for baseline characteristics.

Harms of index test and consequences of testing. PET was associated with significantly lower exposure to radiation at the index visit compared with SPECT (mean 4.0 vs. 11.0 mSv; $p < 0.0001$).⁸⁹

Harms of additional testing. Compared with SPECT, the mean total radiation exposure over the 24 month study period was significantly lower following PET (6.0 vs. 11.6 mSv; $p < 0.0001$).⁸⁹ However, during followup, radiation exposure was higher in the group initially tested with PET than with SPECT (2.0 vs. 0.6 mSv; $p < 0.0001$).⁸⁹

Differential effectiveness or safety in subgroups. No analyses related to differential effectiveness or safety of PET versus SPECT with regard to patient characteristics or other factors were provided.

Anatomic Tests Versus Functional Tests

CCTA Versus SPECT

One poor-quality trial compared CCTA with SPECT in 180 patients at intermediate to high pretest risk presenting with stable chest pain and suspected CAD at one of two outpatient cardiology clinics in the United States (Appendix E, Tables E14–E15)⁸⁰; no other studies compared anatomical and functional testing in this population. The trial was funded by grants from GE Healthcare and Vital Images. Outcomes for 98.3% of patients were reported at a mean of 1.8 ± 1.1 months. CCTA scans were obtained with a 64-detector row CT scanner and iodinated contrast. Rest-stress SPECT employed exercise or pharmacological stress though the percentage of patients who received each type of stress was not reported. No patients had a history of MI, known CAD, or prior revascularization as per inclusion requirements. CCTA patients were slightly younger (mean age 56 vs. 59), more likely to be male (58% vs. 43%) and have typical angina (32% vs. 23%) than SPECT patients. The percentage of patients with atypical or noncardiac angina were similar across groups. CCTA patients were more likely to be at high pretest risk (33% vs. 24%), though there were no differences between groups in intermediate (63% vs. 67%) or low (4% vs. 9%) risk. Pretest Framingham risk estimates were

similar between CCTA and SPECT groups (mean score 18.3 vs. 19.2). Methodological shortcomings included unclear methods for randomization and unclear allocation concealment, lack of blinded outcomes assessment and significant baseline differences between groups. It was not clear whether both groups had similar length of followup.

Clinical outcomes: All outcomes are reported at the mean followup of 1.8 ± 1.1 months, which correlates to approximately 1 to 3 months.⁸⁰ No patient died or had an MI in either group. The frequency of CAD-related hospitalization was similar between the CCTA and SPECT groups (12% vs. 11%). Test results were positive (abnormal) in 30% of CCTA and 36% of SPECT patients; the remaining patients tested negative. There were no differences between groups in the mean change from baseline of any subscale of the Seattle Angina Questionnaire (SAQ), including quality of life/disease perception, physical limitation, angina stability, angina frequency, and treatment satisfaction subscales. Clinical outcomes for test-positive versus test-negative patients were not reported.

Clinical management. ICA referral rates were higher following CCTA versus SPECT (13% vs. 8%, RD 5, 95% CI -4 to 14 per 100) through a mean of 1.8 ± 1.1 months, though the difference did not reach statistical significance.⁸⁰ Fewer CCTA patients had any additional noninvasive cardiac imaging test during the followup period but the result was not significant (3% vs. 10%, RD -7, 95% CI -14 to 0.4 per 100). However, CCTA patients were more likely to undergo subsequent revascularization (CABG or PCI) (8% vs. 1%, RD 6.6, 95% CI 0.7 to 12.5 per 100) during followup. Compared with baseline use, more CCTA patients used aspirin (within-person change from baseline: 22% vs. 8%, $p=0.04$) and statin (within-person change from baseline: 7% vs. -3.5%, $p=0.03$) during followup than SPECT patients, however there was no difference between groups in the within-person change in other medications (nonstatin lipid lowering medications, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor antagonists, or calcium channel blockers). Overall, initial testing with CCTA is more likely to result in coronary revascularization and more aggressive medical therapy than initial testing with SPECT.

Harms of index test and consequences of testing. CCTA was associated with significantly lower exposure to radiation at the index visit compared with SPECT: median (interquartile range [IQR]) 6.5 (5.1 to 13.3) versus 13.3 (13.1 to 38.0) mSv; $p<0.0001$.

Harms of additional testing. Compared with SPECT, the median total radiation exposure over the 1.8-month followup period was significantly lower following PET (7.3 [IQR, 5.1 to 13.7] vs. 13.3 [IQR, 13.1 to 38.0] mSv, $p<0.0001$); however, during followup, radiation exposure was higher in the group initially tested with PET than with SPECT (0.8 vs. 0 mSv). *Differential effectiveness or safety in subgroups.* No analyses related to differential effectiveness or safety of PET versus SPECT with regard to patient characteristics or other factors were provided.⁸⁰

Noncomparative Studies: Functional

No noncomparative studies of anatomical testing in patients at intermediate to high risk met the inclusion criteria that reported outcomes of interest. For functional testing in this population, only studies of stress echocardiography were identified.

Stress echocardiography. One noncomparative study of stress echocardiography in patients at low to intermediate pretest risk reported on predictive accuracy.¹⁰⁴ This study enrolled 244 women with a mean age of 60 ± 10 years, and employed either exercise or pharmacological (70% dipyridamole; 30% dobutamine) stress in an outpatient setting. Atypical as opposed to typical angina was more common (63% vs. 36%). The frequency of any cardiac event over a

mean of 36 months was substantially higher in those who had a positive compared to a negative result on stress echocardiography (33 vs. 2 per 100 people (Appendix F, Tables F11–F12).

Table 10. Summary of findings and strength of evidence: Intermediate to high pretest risk

Outcome*	Comparison	Number of Studies (N)	Setting	Conclusions	Strength of Evidence
Mortality (all-cause)	PET vs. SPECT	1 observational N=1113	Hospital and outpatient centers	Through 24 months, mortality was more common in PET than SPECT patients (5.5% vs. 1.6%, unadjusted RR 3.4, 95% CI 1.6 to 7.2). Definitive conclusions are not possible [†]	Insufficient
	CCTA vs. SPECT	1 RCT N=180	Outpatient	There were no deaths in either group through a mean of 55 days followup. Definitive conclusions are not possible [†]	Insufficient
Myocardial Infarction	PET vs. SPECT	1 observational N=1113	Hospital and outpatient centers	The frequency of MI was similar between groups: 1.1% (PET) versus 1.2% (SPECT). Definitive conclusions are not possible [†]	Insufficient
	CCTA vs. SPECT	1 RCT N=180	Outpatient	There were no MIs in either group through a mean of 55 days followup. Definitive conclusions are not possible [†]	Insufficient
Invasive Coronary Angiography Referral	PET vs. SPECT	1 observational N=1113	Hospital and outpatient centers	PET was associated with significantly more ICA referrals through 90 days (11% vs. 4%, adjusted OR 5.03, 95% CI 1.04 to 24.43) and 24 months (15.0% vs. 6.7%, unadjusted RR 2.2, 95% CI 1.5 to 3.2, p<0.0001). Definitive conclusions are not possible [†]	Insufficient
	CCTA vs. SPECT	1 RCT N=180	Outpatient	Strength of evidence is low that difference in ICA referral was no found: CCTA versus SPECT (13% vs. 8%, RD 5, 95% CI -4 to 14 per 100, p=NS) through a mean of 55 days.	Low
Revascularization	PET vs. SPECT	1 observational N=1113	Hospital and outpatient centers	Revascularization was performed more frequently following PET at both 90 days (7% vs. 1.4%, RR 3.5, 95% CI 1.7 to 7.0) and 24 months (8% vs. 2.4%, RR 3.3, 95% CI 1.8 to 6.1). Definitive conclusions are not possible [†]	Insufficient
	CCTA vs. SPECT	1 RCT N=180	Outpatient	CCTA was associated with more revascularizations than SPECT (8% vs. 1%, RD 6.6%, 95% CI 0.7% to 12.5%) through a mean of 1.8 months.	Low
Percutaneous Coronary Intervention	PET vs. SPECT	1 observational N=1113	Hospital and outpatient centers	PCI was performed more frequently following PET through 90 days (4.6% vs. 1.4%, RR 3.2, 95% CI 1.5 to 7.1) and 24 months (5.7% vs. 1.8%, RR 2.9, 95% CI 1.5 to 5.7). Definitive conclusions are not possible [†]	Insufficient

Outcome*	Comparison	Number of Studies (N)	Setting	Conclusions	Strength of Evidence
Coronary Artery Bypass Graft	PET vs. SPECT	1 observational N=1113	Hospital and outpatient centers	CABG was performed slightly more frequently following PET at the index visit (1.6% vs. 0.4%, RR, 4.6, 95% CI 1.007 to 21.4) and through 24 months (2.0% vs. 0.4%, RR 5.7, 95% CI 1.3 to 25.5). Definitive conclusions are not possible†	Insufficient
Additional Testing	CCTA vs. SPECT	1 RCT N=180	Outpatient	There is low strength of evidence that a difference in use of additional testing was not found. Fewer CCTA patients had additional noninvasive cardiac imaging test through a mean of 1.8 ± 1.1 months though the result was not significant (3% vs. 10%, RD -7, 95% CI -14 to 0.4 per 100).	Low
Hospitalization (Cardiac related)	CCTA vs. SPECT	1 RCT N=180	Outpatient	CAD-related hospitalization was similar between the CCTA and SPECT groups (12% vs. 11%) through a mean of 1.8 months	Low

CABG = coronary artery bypass graft; CAD = coronary artery disease; CCTA = coronary computed tomography angiography; CI = confidence interval; ICA = invasive coronary angiography; NS = not statistically significant; PCI = percutaneous coronary intervention; PET = positron emission tomography; RCT = randomized controlled trial; RD = risk difference; RR = relative risk; SPECT = single photon emission computed tomography.

*Primary outcomes not listed in this table had no evidence and thus insufficient strength of evidence.

†Definitive conclusions are not possible due to study limitations and/or imprecision in observational studies or lack of data in RCTs.

High Pretest Risk of Coronary Artery Disease

Key Points

Given the focus of the report on evaluation of testing based on pretest risk, results for the high pretest risk groups are presented below even though evidence from these groups was rated as insufficient.

CCTA Versus Usual Care

- In a small subgroup of high-risk patients presenting to the ED, there was insufficient evidence from one small fair-quality trial to draw conclusions regarding 1-month mortality between groups, hospitalization for acute coronary syndrome, ICA referral, and revascularization.

SPECT Versus Exercise ECG

- In a small subgroup of high-risk outpatients, there was insufficient evidence that ICA referral was less common in SPECT compared with the exercise ECG group; data also suggests that additional noninvasive imaging following SPECT may be less common, though the sample size was too small to reach statistical significance (insufficient evidence).

Detailed Synthesis

A total of three studies were identified in populations with high pretest risk of CAD and two included the following comparisons: CCTA versus usual care (1 RCT)⁷¹ and SPECT versus exercise ECG (1 RCT)⁸¹ (Table 11); one additional noncomparative study reported on the predictive accuracy of stress echocardiography.¹¹⁵

Anatomic Tests Versus Usual Care

CCTA Versus Usual Care

One fair-quality RCT compared CCTA with usual care in high-risk patients⁷¹ (Appendix E, Tables E1–E3, E10–E13, E18–E21, E36, E40, G3); no other studies compared anatomical testing with usual care in this population. The trial enrolled 266 patients presenting with chest pain to a single ED in South Korea. Study funding was not reported. Results were stratified based on pretest risk, with 56 of the 266 patients at high pretest risk. CCTA was performed with 64-slice scanning (n=28); usual care consisted of a conventional diagnostic strategy (e.g., serial ECGs, cardiac biomarkers) (n=28). Subsequent diagnostic tests were done at the discretion of the treating physician. Overall, groups were similar in age (mean 57.5 years), sex (38.7% female), and cardiac risk factors, however these characteristics were not compared for high-risk patients only. Baseline risk scores were not reported. Outcomes were reported at the index visit and at 1 month of followup. Methodological shortcomings included unclear randomization method, allocation concealment, and blinding of outcomes assessment.

Clinical outcomes. No deaths were reported in any high-risk patients through 1 month of followup.⁷¹ Patients in the CCTA group were less likely to be hospitalized for any reason at the index ED visit compared with the usual care group (79% vs. 100%, RD -21, 95% CI -37 to -6 per 100), but unnecessary hospitalizations at the index visit were similar between groups (18% vs. 21%). Hospitalization for acute coronary syndrome occurred in fewer CCTA patients, though the difference was not statistically significant (57% vs. 64%, RD -07, 95% CI -33 to 18 per 100). Of the patients hospitalized for acute coronary syndrome, CCTA patients were less likely to be admitted for NSTEMI (14% vs. 29%, RD -14, 95% CI -35 to 7 per 100) and more likely to be admitted for unstable angina (43% vs. 36%, RD 7, 95% CI -18 to 33 per 100); the results were not statistically significant due to the small study size. Clinical outcomes for test-positive versus test-negative patients were not reported.

Clinical management. A lower proportion of CCTA patients underwent ICA during the index ED visit compared with usual care patients (75% vs. 93%, RD -18, 95% CI -37 to 0.8); the result was nearly statistically significant (p=0.0714). No high risk usual care patients (0/28) underwent additional noninvasive stress testing; the proportion of those having additional stress testing was not reported for the high risk CCTA group. Revascularization was performed in somewhat fewer CCTA patients compared with usual care patients (43% vs. 50%, RD -7, 95% CI -33 to 19 per 100).⁷¹

Harms of index test and consequences of testing, harms of additional testing, and differential effectiveness or safety in subgroups. Not reported for the high pretest risk subgroup.

Functional Tests Versus Functional Tests

SPECT Versus Exercise ECG

One fair-quality trial compared SPECT with exercise ECG in high-risk patients (Appendix E, Tables E1–E3, E10–E13, E18–E21, E36, E40, G3); no other studies compared different types of functional testing in this population.⁸¹ The trial included 457 patients referred for stable chest pain to a single outpatient center in the United Kingdom; grants were received from Bristol-Myers Squibb and Northwick Park Cardiac Research, as well as from an individual. Results were stratified based on pretest risk; 106 patients had high pretest likelihood of CAD. Patients underwent either SPECT (n=45) or exercise ECG (n=61). Treadmill exercise was employed in both groups; pharmacological stress was employed in some patients receiving SPECT. Groups were similar overall in age (mean age 59 years), sex (43.5% female), and cardiac risk factors but were not compared within the high risk group. Baseline risk scores were not reported. Outcomes were reported for 96.9% of patients over a mean of 22 months. Methodological shortcomings included lack of allocation concealment and lack of blinded outcome assessment.

Clinical outcomes. Not reported for high-risk patients.

Clinical management. ICA referral through 22 months occurred in significantly fewer SPECT than exercise ECG patients (44% vs. 85%, RD -41, 95% CI -58 to -24 per 100). This trial used Bayesian methods to model posttest risk and reported that 77 percent of those with high pretest risk finished with high posttest risk (SPECT 56% vs. ECG 93%) and that those with a normal or low risk test in either arm did not receive ICA. Additional noninvasive imaging was performed somewhat less frequently in patients who underwent SPECT compared with exercise ECG (0% vs. 5%, RD -5, 95% CI -10 to 1 per 100), but the difference was not statistically significant. Medication therapy was prescribed significantly more often in the SPECT group based on initial test results (56% vs. 10%, RD 46, 95% CI 29 to 62 per 100).

Harms of index test and consequences of index and additional testing; differential effectiveness or safety in subgroups. Not reported for high-risk patients.

Noncomparative Studies

No noncomparative studies of anatomical or functional noninvasive tests were identified that reported on predictive accuracy in high pretest risk patients.

Table 11. Summary of findings and strength of evidence: High pretest risk

Outcome*	Comparison	Number of Studies (N)	Setting	Conclusions	Strength of Evidence
Mortality (all-cause)	CCTA vs. Usual Care†	1 RCT (n=56 in high-risk subgroup)	ED	No deaths through 1 month in either group. Definitive conclusions are not possible.‡	Insufficient
Invasive Coronary Angiography Referral	CCTA vs. Usual Care†	1 RCT (n=56 in high-risk subgroup)	ED	At the index visit, fewer CCTA patients underwent ICA (75% vs. 93%, RD -18, 95% CI -37 to 0.8, p=0.0714). Definitive conclusions are not possible.‡	Insufficient
	SPECT vs. exercise ECG	1 RCT (n=106 in high-risk subgroup)	Outpatient	ICA was less common following SPECT versus exercise ECG through a mean of 22 months (44% vs. 85%, RD -41, 95% CI -58 to -24 per 100). Definitive conclusions are not possible.‡	Insufficient
Revascularization	CCTA vs. Usual Care†	1 RCT (n=56 in high-risk subgroup)	ED	Revascularization frequencies at the index visit were: CCTA (43%) vs. usual care (50%) (RD -7, 95% CI -33 to 19 per 100, p=NS). Definitive conclusions are not possible.‡	Insufficient
Additional Testing	SPECT vs. exercise ECG	1 RCT (n=106 in high-risk subgroup)	Outpatient	Additional testing through a mean of 22 months was: SPECT (0%) vs. ECG (5%), RD -5, 95% CI -10 to 1 per 100, p=NS). Definitive conclusions are not possible.‡	Insufficient
Hospitalization (Cardiac related)	CCTA vs. Usual Care†	1 RCT (n=56 in high-risk subgroup)	ED	Hospitalization for acute coronary syndrome at the ED index visit were: CCTA (57%) vs. usual care (64%), RD -07, 95% CI -33 to 18 per 100, p=NS). Definitive conclusions are not possible.‡	Insufficient

CCTA = coronary computed tomography angiography; CI = confidence interval; ECG = electrocardiography; ED = emergency department; ICA = invasive coronary angiography; NS = not statistically significant; RCT = randomized controlled trial; RD = risk difference; SPECT = single photon emission computed tomography.

*Primary outcomes not listed in this table had no evidence and thus insufficient strength of evidence.

†Usual care consisted of a conventional diagnostic strategy using serial ECGs and cardiac biomarkers.

‡Definitive conclusions are not possible due to lack of data from subgroup analyses in RCTs.

Mixed Population: Pretest Risk Not Reported or Results Not Stratified by Risk

Key Points

Evidence for all primary outcomes and comparators not listed below was insufficient to draw conclusions due to study limitations and/or imprecision in the observational study or due to lack of evidence.

CCTA Versus Usual Care

- In a population presenting to the ED and not stratified by risk (one fair-quality trial), there was low strength of evidence that a difference between groups was not found in 1-month MI or contrast-induced nephropathy.

SPECT Versus Exercise ECG

- In outpatients not stratified by risk, there was low strength of evidence from one trial that a difference was not found between groups in all-cause mortality or MI through a mean of 22 months, while SPECT was associated with fewer revascularizations than exercise ECG.

Exercise ECG Versus Nuclear MPI

- Low strength of evidence from a large administrative database of mixed risk-level Medicare outpatients suggested that 6-month mortality was similar between groups. Patients who underwent exercise ECG were less likely to undergo ICA through 6 months than those who were tested with MPI; revascularization (including CABG and PCI evaluated separately) was performed similarly between groups (low strength of evidence for both).

Stress Echocardiography Versus Nuclear MPI

- Low strength of evidence from a large administrative database of mixed risk-level Medicare outpatients suggested that 6-month mortality was similar between groups. Through 6 months, ICA referral was statistically less frequent in the stress echocardiography group, while additional noninvasive testing was slightly more common in this group (low strength of evidence). There were no apparent clinical differences between groups in referral for revascularization (including CABG and PCI evaluated separately) (low strength of evidence).

CCTA Versus Exercise ECG

- One fair-quality trial of ED patients at various pretest risk levels with 12 months followup found low strength of evidence that a difference between groups was not found in all-cause mortality or MI, while there was moderate-strength evidence that cardiac-related hospitalizations were less common in the CCTA group. CCTA was associated with more ICAs and more revascularizations (including PCI), though CABG was utilized similarly between groups (low strength of evidence).

CCTA Versus Nuclear MPI

- One large fair-quality database study of mixed risk-level Medicare outpatients provided low-strength evidence that all-cause mortality was similar through 6 months. CCTA patients were more likely to undergo ICA, additional noninvasive testing, and revascularization (including PCI and CABG evaluated separately) through 6 months (low strength of evidence).
- One fair-quality registry study provided low-strength evidence that revascularization was more common following CCTA through a median of 1.42 years; the setting was not reported.

Detailed Synthesis

A total of 18 studies were identified in populations with mixed pretest risk of CAD or for which risk was not reported; nine included the following comparisons (one administrative database study reported outcomes for six different test comparisons): CCTA versus usual care (1 RCT),⁷¹ exercise ECG (1 RCT,⁷⁸ 1 administrative database⁹⁶), SPECT (1 prospective

registry,⁹⁸ 1 administrative database⁹¹), nuclear MPI (1 prospective observational,⁹⁹ 1 administrative database⁹⁶), and stress echocardiography (1 administrative database)⁹⁶; SPECT versus exercise ECG (1 RCT,⁸¹ 1 administrative database⁹⁶); and stress echocardiography versus exercise ECG (1 RCT,⁸² 1 prospective observational,⁹⁰ 1 administrative database⁹⁶) and SPECT (1 administrative database)⁹⁶ (Tables 12–14). Four additional noncomparative studies (one reported data for two separate tests) reported on the predictive accuracy of stress echocardiography (2 studies),^{109, 113} stress ECG (2 studies)^{107, 109}, and calcium scoring (1 study)¹¹⁷; and five studies were included for safety only following CT (2 prospective observational)^{92, 93} and stress echocardiography (2 prospective,^{85, 95} 1 retrospective observational⁹⁷).

Anatomic Tests Versus Usual Care

CCTA Versus Usual Care

One fair-quality RCT compared CCTA with usual care in patients combined across three pretest risk levels (low 37%, intermediate 42%, high 21%) (Appendix E, Tables E1–E3, E10–E13, E18–E21, E36, E40, G3). Only those results not stratified by pretest risk level (which are reported in the appropriate sections) are reported here. The trial enrolled 266 patients presenting with chest pain to a single ED in South Korea.⁷¹ Study funding was not reported. CCTA was performed with 64-slice scanning (n=133); usual care consisted of a conventional diagnostic strategy (e.g., serial ECGs, cardiac biomarkers) (n=133). Subsequent diagnostic tests were done at the discretion of the treating physician. Overall, groups were similar in age (mean 57.5 years), sex (38.7% female), and cardiac risk factors. Baseline risk score were not reported. Outcomes were reported at the index visit and at 1 month of followup. Methodological shortcomings included unclear randomization method, allocation concealment, and blinding of outcomes assessment.

Clinical outcomes. Through 1-month followup, no patients in the CCTA group and one patient in the usual care group experienced a nonfatal MI during the 1-month followup period (0% vs. 0.8%, p=0.32).⁷¹

Clinical management. Ten percent of CCTA patients underwent additional noninvasive stress testing after the index visit and through 30 days. In the usual care group, noninvasive testing was done at the discretion of the physician in 50 percent of patients at the index visit. Because this is a first test in the usual care patients, it is not considered “additional” noninvasive testing.⁷¹

Harms of index test and consequences of testing. No incidence of contrast-induced nephropathy was reported in either group. Following imaging with CCTA, two patients (1.5%) developed a diffusing, irritating skin rash which resolved spontaneously; radiation exposure averaged 12.5 ± 2.0 mSv in this group (not reported for the usual care group).⁷¹

Harms of additional testing, differential effectiveness or safety in subgroups. Not reported for this population.

Table 12. Summary of findings and strength of evidence: Mixed pretest risk-anatomical testing versus usual care

Outcome*	Comparison	Number of Studies (N)	Setting	Conclusions	Strength of Evidence
Myocardial infarction	CCTA vs. Usual Care [†]	1 RCT (N=266)	ED	There was low-strength evidence a difference in MI was not found. Through 30 days, no patient in the CCTA group had a myocardial infarction versus one in the usual care group (0% vs. 0.8%).	Low
Harms of the Index Test	CCTA vs. Usual Care [†]	1 RCT (N=266)	ED	There were no cases of contrast-induced nephropathy between groups.	Low

CCTA = coronary computed tomography angiography; ED = emergency department; RCT = randomized controlled trial.

*Primary outcomes not listed in this table had no evidence and thus insufficient strength of evidence.

[†]Usual Care consisted of a conventional diagnostic strategy using serial ECGs and cardiac biomarkers.

Functional Tests Versus Functional Tests

SPECT Versus Exercise ECG

One fair-quality RCT compared SPECT with exercise ECG and enrolled patients at various pretest risk levels (low 16%, intermediate 61%, high 23%) presenting with stable chest pain at a single outpatient center in the United Kingdom (Appendix E, Tables E1–E3, E10–E13, E18–E21, E36, E40, G3).⁸¹ Only those results not stratified by pretest risk level (which are reported in the appropriate sections) are reported here. This trial was funded by unrestricted grants from Bristol-Myers Squibb Medical Imaging, Northwick Park Cardiac Research Fund, and from an individual. A symptom limited Bruce or modified Bruce exercise protocol was used in 62 percent of patients undergoing SPECT (n=250) and 100% undergoing ECG testing (n=207); the remaining SPECT patients received dipyridamole infusion unless there was a contraindication in which case dobutamine stress was performed. The two groups were similar with regard to mean age (59 years) and sex (44% female), but more patients in the SPECT group were Caucasian (56% vs. 47%) and were more likely to have hypertension (53% vs. 46%) and diabetes (19% vs. 14%). The pretest likelihood of CAD differed substantially in subjects undergoing SPECT versus exercise ECG: low (11% vs. 21%), intermediate (71% vs. 49%), and high (18% vs. 29%). Baseline risk scores were not reported. Outcomes were reported for 96.9% of patients over a mean of 22 months. Methodological concerns included lack of concealed of allocation and uncertainty regarding blinded assessment of outcomes.

Clinical outcomes. Overall mortality was very low in both SPECT and exercise ECG groups through a mean of 22 months followup (0.8% vs. 0.9%). MI through the same followup occurred in no SPECT patients and one exercise ECG patient (0% vs. 0.5%); this event was fatal.⁸¹

Clinical management. ICA referral was significantly less following SPECT (16% vs. 47%; RD -30.9, 95% CI -39.2 to -22.7) and results showed false positives (i.e., no obstructive disease) in fewer SPECT patients (17.1% vs. 36.7%). Fewer patients who had SPECT as the index test underwent revascularization compared to those who had an exercise ECG as their index test (10.8% vs. 17.9%, RD -7.1, 95% CI -13.6 to -0.6 per 100).⁸¹

Harms of index test and consequences of testing, harms of additional testing, differential effectiveness or safety in subgroups. Not reported in this population.

Exercise ECG Versus Nuclear MPI

One large, fair-quality administrative database study was conducted using a 20 percent random sample of Medicare claim records from 2006 to 2008 (N=282,830)⁹⁶; patients could receive one of four tests including and exercise ECG (n=61,063) and MPI (n=132,343) (Appendix E, Tables E4–E9, E40, G3). Included claims were limited to those in an outpatient setting for patients aged 66 years or older; no patient had a history of known CAD (within the previous 9 months) or prior MI or revascularization (within the previous 12 months). This study was designed to evaluate CCTA, but the data provided allowed some comparisons across the other tests. No test details were reported, to include information regarding how a test was chosen for a given patient; only CPT (Current Procedural Terminology) codes that included both and stress (exercise and pharmacological) ECG and stress SPECT and PET were provided. Pretest CAD risk and other baseline risk scores were not reported. Exercise ECG patients were slightly younger than MPI patients (mean age 73.1 vs. 75.7 years), slightly less likely to be female (49.0% vs. 54.5%), and had significantly fewer risk factors and comorbidities. Outcomes were reported at 6 months and adjusted for confounding baseline variables. This study was funded by the American Heart Association. Methodological limitations included lack of blinded outcomes assessment and significant baseline differences between groups, although these differences were controlled for with the adjusted risk estimates.

Clinical outcomes. The 6-month risk of death from any cause was similar between exercise ECG and MPI (0.78% vs. 1.28%, adjusted OR 0.93, 95% CI 0.83 to 1.04) as was the risk of hospitalization for acute MI (0.32% vs. 0.43%, adjusted OR 0.86, 95% CI 0.72 to 1.03).⁹⁶ Clinical outcomes for test-positive versus test-negative patients were not reported.

Clinical management. Lower 6-month ICA referral rates were reported following exercise ECG compared with MPI (9.04% vs. 12.13%, adjusted OR 0.72, 95% CI 0.70 to 0.75). Any additional noninvasive testing through 6 months was significantly more common in ECG versus MPI patients (19.34% vs. 3.22%, adjusted OR 7.46, 95% CI 7.16 to 7.77); this difference was statistically significant for all types of noninvasive tests employed (MPI, stress echocardiography, exercise ECG) except CCTA. The need for any revascularization through 6 months was similar between groups although the difference was statistically meaningful (4.31% vs. 4.59%, respectively; adjusted OR 0.90, 95% CI 0.85 to 0.94); this trend held true for both PCI (2.57% vs. 3.37%, adjusted OR 0.72, 95% CI 0.68 to 0.77) and CABG (1.82% vs. 1.29%, adjusted OR 1.37, 95% CI 1.26 to 1.49). Although fewer patients underwent ICA in the exercise ECG group, they were significantly more likely to receive revascularization following ICA than MPI patients (46.49% vs. 37.53%, adjusted OR 1.30, 95% CI 1.21 to 1.40).

Harms of index test and consequences of testing and harms of additional testing. No harms related to either the index or additional testing were reported.

Differential effectiveness or safety in subgroups. No analyses related to differential effectiveness or safety of nuclear MPI and exercise ECG with regard to patient characteristics or other factors were provided; however the database study focused on Medicare beneficiaries (age \geq 66 years).⁹⁶

Stress Echocardiography Versus Exercise ECG

One poor-quality RCT⁸² and two observational studies, one fair-quality⁹⁶ and one poor-quality,⁹⁰ were identified that compared stress echocardiography to exercise ECG (Appendix E, Tables E1–E9, E40, G3).

The RCT compared dobutamine (n=47) and exercise stress echocardiography (n=57), and exercise ECG (n=54) in women with chest pain who had no history of cardiac disease but who had at least two cardiac risk factors.⁸² Patients were recruited from family medicine, emergency departments, and inpatient cardiology (number of sites and locations not reported) and 90.3 percent were followed for a mean of 28.1 ±14.2 months. Ages were similar across groups (mean 54.5 years) as was the proportion of Caucasians (97.5%). Patients in the stress echocardiography groups were more likely to have hypertension than those in the exercise ECG group (53.8% vs. 38.9%); all other relevant cardiac risk factors were similar. Pretest CAD risk and other baseline risk scores were not reported. This trial was funded in part by a clinical research grant from the American Society of Echocardiography. Methodological shortcomings included lack of information on random sequence generation and allocation concealment, lack of information on patients who withdrew after consent, potentially clinically significant baseline differences between groups, and failure to control for possible confounding.

One poor-quality prospective observational study compared exercise stress echocardiography with exercise ECG in patients with suspected or known CAD.⁹⁰ Results were stratified according to history of CAD; therefore, only data for the 5,894 (77.0%) patients without known CAD are included in this report. However, demographics, risk factors, and test details were not reported separately for this subgroup. The study was conducted in the United States at a single large cardiac referral center; choice of test was made according to physician preference and institutional practice. Funding was received from the American Society of Echocardiography and the National Heart Foundation of Australia. Complete followup data were available for all patients for a mean of 33.6 months; however, followup periods differed between the echocardiography and ECG groups (mean 38.4 ± 24 vs. 30 ± 24 months, respectively). Overall, groups were similar in mean age (62 years) and sex (41% female) and there were no statistically significant differences between groups in clinical risk factors. Twelve percent of the patients were considered low risk, 59 percent intermediate, and 29 percent high risk when pretest clinical risk was defined as predicted annualized risk of death or MI. Methodological shortcomings included lack of information regarding blinded outcome assessment and whether baseline risks were similar in the subset of patients with no history of CAD, and unclear reporting of loss-to-followup.

A large, fair-quality administrative database study was conducted using a 20 percent random sample of Medicare claim records from 2006 to 2008 (N=282,830)⁹⁶; patients could receive one of four tests including stress echocardiography (n=80,604) and exercise ECG (n=61,063) and the followup period was 6 months. Pretest CAD risk and other baseline risk scores were not reported. Included claims were limited to an outpatient setting for patients aged 66 years or older; no patient had a history of known CAD (within the previous 9 months) or prior MI or revascularization (within the previous 12 months). This study was designed to evaluate CCTA, but the data provided allowed some comparisons across the other tests. No test details were reported, to include information regarding how a test was chosen for a given patient; only CPT (Current Procedural Terminology) codes that included both stress echocardiography and exercise and pharmacological stress ECG were provided. Both groups were similar in regards to mean age (73.5 years), the proportion of Caucasian patients (88.3%), and relevant cardiac risk factors; however, the stress echocardiography group included more women (57.5% vs. 49.0%). This study was funded by the American Heart Association. Methodological limitations included lack of blinded outcomes assessment and lack of adjustment for differences in age.

Clinical outcomes. The RCT reported that cardiac outcomes (defined as a composite including cardiac death, MI, unstable angina, or coronary angiography demonstrating 50% or more luminal narrowing) occurred similarly following stress echocardiography and exercise ECG (7.7% vs. 7.4%).⁸² When stratified by the result of the test, patients with positive result stress echocardiography results were slightly more likely to have a cardiac outcome than patients with a positive stress ECG (44% [7/16] vs. 38% [3/8]), however the sample size is small. Patients with a negative stress echocardiography result were slightly less likely to have a noncardiac outcome (defined as no cardiac event and/or diagnosis of a noncardiac source of the original pain) than patients with a negative exercise ECG (86% [74/86] vs. 91% [30/33]). Ten of 21 of the patients with a positive test result had a cardiac outcome (positive predictive value 47.6 per 100). The proportion of cases with definitive and accurate results was statistically higher for exercise stress echocardiography than exercise ECG (84% vs. 67%, RD 17, 95% CI 3 to 31). The poorer performance of the exercise ECG was driven by the number of inconclusive tests rather than inaccurate results.

The prospective observational study reported adjusted cardiac death and a composite of death or MI split according to three categories of posttest risk, namely low, intermediate, and high.⁹⁰ Through a mean of 34 months followup, adjusted rates stratified by low, intermediate, and high posttest risk were consistently and statistically lower in the exercise echocardiography group versus the exercise ECG group for both cardiac death (0.4% vs. 0.9%; 1.3% vs. 1.4%; 2.5% vs. 2.9%) and for the composite of death or MI (1.6% vs. 1.8%; 2.2% vs. 3.4%; 4.6% vs. 5.5%) ($p < 0.006$).

The database study of Medicare claims reported that the 6-month risk of death from any cause was somewhat higher following stress echocardiography than exercise ECG (0.95% vs. 0.78%, unadjusted RR 1.21, 95% CI 1.08 to 1.35).⁹⁶ Hospitalization for acute MI was the same (0.32%) for both groups.

Clinical management. The RCT reported that additional pharmacological stress echocardiography was performed due to indeterminate test results in significantly fewer exercise echocardiography patients than exercise ECG patients (4% vs. 24%, RD -21, 95% CI -33 to -8 per 100).⁸² This is not reported for the patients randomized to pharmacologic stress echocardiography as the initial test, as this test was considered definitive and no patients in this group were referred for additional testing per protocol. All of the second tests were negative; no other information was provided on followup treatment or testing.

The prospective study found that through a mean of 34 months, ICA was performed in a similar percentage of stress echocardiography patients at low (6% vs. 8%) and intermediate posttest risk (12% vs. 14%); however ICA was more common following stress echocardiography in those considered to be at high posttest risk (40% vs. 28%, $p < 0.0001$).⁹⁰ The pattern was the same for revascularization (low posttest risk 5% vs. 7%; intermediate 8% vs. 9% and high 29% vs. 20%), including PCI (low posttest risk 4% vs. 6%; intermediate 5% vs. 6%; high 22% vs. 12%). However, the pattern was different in terms of referral for CABG, with similar results following stress echocardiography between all posttest risk groups: low (1% vs. 2%), intermediate (3% in both groups), and high posttest risk (6% vs. 8%).

In the database study on Medicare claims, there was no difference between groups in referral for ICA (9.50% vs. 9.04%, unadjusted RR 1.05, 95% CI 1.02 to 1.09), although the result was statistically significant.⁹⁶ In the patients referred for ICA, fewer stress echocardiography patients received revascularization (43.65% vs. 46.49%, unadjusted RR 0.94, 95% CI 0.90 to 0.98). Referral for any additional noninvasive cardiac test was done in fewer stress echocardiography

than exercise ECG patients in the 6 months following initial testing (5.57% vs. 19.34%, unadjusted RR 0.29, 95% CI 0.28 to 0.30). The need for any revascularization in the same time period was similar between groups (4.22% vs. 4.31%); this was also true for PCI (2.61% vs. 2.57%) and CABG (1.69% vs. 1.82%).

Harms of index test and consequences of testing. No information on harms was provided by the above studies. However, three additional studies were identified in the population of interest comparing stress echocardiography with exercise ECG that reported complications. There were no incidences of major periprocedural side effects or complications in either group (all patients had both tests) as reported by two large studies (N=429 and 244 women).^{95, 104} Two studies reported side effects for the echocardiography group only; all patients underwent dipyridamole stress. One study⁸⁵ reported chest pain (37%), flushing (22%), headache (30%), dyspnea (11%), hypotension (6.4%), nausea (5.5%), dizziness (4.5%), and ST segment depression in 109 of 130 patients and the other reported low incidences of excessive tachycardia with palpitations (0.2%) and hypotension and symptomatic bradycardia (0.5%) in their population (N=429).⁹⁵

Harms or consequences of additional testing. None of the three studies reported harms or consequences of additional testing.

Differential effectiveness or safety in subgroups. No analyses related to differential effectiveness or safety of stress echocardiography and exercise ECG with regard to patient characteristics or other factors were provided, however the trial enrolled only women⁸² and one focused on Medicare beneficiaries.⁹⁶

Stress Echocardiography Versus Nuclear MPI

Only one fair-quality study compared stress echocardiography to nuclear MPI; pretest risk was not reported (Appendix E, Tables E4–E9, E40, G3). Shreibati et al. conducted a large administrative database study using a 20 percent random sample of Medicare claim records from 2006 to 2008 (N=282,830); patients could receive one of four tests including stress echocardiography (n=80,604) and MPI (n=132,343).⁹⁶ Pretest CAD risk and other baseline risk scores were not reported. Claims were limited to those in an outpatient setting for patients aged 66 years or older; no patient had a history of known CAD (within the previous 9 months) or prior MI or revascularization (within the previous 12 months). This study was designed to evaluate CCTA, but the data provided allowed some comparisons across the other tests. No test details were reported, to include information regarding how a test was chosen for a given patient; only CPT (Current Procedural Terminology) codes that included both stress echocardiography and stress SPECT and PET were provided. Patients in the stress echocardiography and MPI groups were similar, respectively, in terms of mean age (73.8 vs. 75.7 years), sex (57.5% vs. 54.5% female), and race (89.1% vs. 89.3% Caucasian). However, those who underwent stress echocardiography group had significantly fewer reported cardiac risk factors (i.e., diabetes 20.8% vs. 31.6%; hyperlipidemia 64.6% vs. 74.8%; hypertension 60.2% vs. 74.9%). Outcomes were reported at 6 months and adjusted for confounding baseline variables. This study was funded by the American Heart Association. Methodological limitations included lack of blinded outcomes assessment and significant baseline differences between groups.

Clinical outcomes. In this study of Medicare claims, the 6-month risk of death from all causes was similar for stress echocardiography and MPI (0.95% vs. 1.28%, adjusted OR 1.00, 95% CI 0.90 to 1.10), as was the rate of hospitalization for acute MI (0.32% vs. 0.43%, adjusted OR 0.83, 95% CI 0.70 to 0.98) although the results were statistically significant.⁹⁶

Clinical management. Through 6 months followup, referral for ICA was significantly less frequent following stress echocardiography (9.50% vs. 12.13%; adjusted OR 0.78, 95% CI 0.76 to 0.81). The need for any revascularization in the same time period was similar between groups (4.22% vs. 4.59%, adjusted OR 0.93, 95% CI 0.88 to 0.98); this was true for both PCI (2.61% vs. 3.37%, adjusted OR 0.76, 95% CI 0.72 to 0.81) and CABG (1.69% vs. 1.29%, adjusted OR 1.40, 95% CI 1.29 to 1.52). In the patients referred for ICA, more stress echocardiography patients received revascularization (43.65% vs. 37.53%, adjusted OR 1.23, 95% CI 1.15 to 1.32). Referral for any additional noninvasive cardiac test was somewhat more frequent in stress echocardiography patients (5.57% vs. 3.22%; adjusted OR 1.92, 95% CI 1.83 to 2.0).⁹⁶

Harms of index test and consequences of testing. No information on harms was provided by the above study. However, one additional study was identified in the population of interest that compared dobutamine stress echocardiography with single photon emission computed tomography (SPECT) and reported complications for the echocardiography arm only (n=70).⁹⁷ Overall, there were no serious side effects including sustained arrhythmia, severe hypotension, or myocardial infarction. Reported complications included: chest pain requiring test termination (11%), extracardiac side effects (e.g., dyspnea, nausea) (5.7%), increased blood pressure (2.9%), and multiple ventricular ectopy (1.4%).

Harms of additional testing: Not reported.

Differential effectiveness or safety in subgroups. No analyses related to differential effectiveness or safety of stress echocardiography and MPI with regard to patient characteristics or other factors were provided, however the database study included only Medicare patients.

Table 13. Summary of findings and strength of evidence: Mixed pretest risk- functional versus functional testing

Outcome*	Comparison	Number of Studies (N)	Setting	Conclusions	Strength of Evidence
Mortality (all-cause)	SPECT vs. Exercise ECG	1 RCT (N=457)	Outpatient	There was low-strength evidence a difference in mortality was not found; frequency by 22 months was 0.8% versus 0.9% for SPECT and exercise ECG, respectively.	Low
	Exercise ECG vs. Nuclear MPI	1 observational (N=193,406 Medicare)	Outpatient	Frequency of mortality was similar between groups through 6 months (0.78% vs. 1.28%, adjusted OR 0.93, 95% CI 0.83 to 1.04).	Low
	Stress echocardiography vs. Exercise ECG	1 observational (n=5894 with no known CAD)	Outpatient	Through a mean of 34 months followup, adjusted rates stratified by low, intermediate, and high posttest risk were consistently and statistically lower in the exercise echocardiography group versus the exercise ECG group for cardiac death (0.4% vs. 0.9%; 1.3% vs. 1.4%; 2.5% vs. 2.9%, p<0.006). Definitive conclusions are not possible.†	Insufficient
	Stress echocardiography vs. Exercise ECG	1 observational (N=141,667 Medicare)	Outpatient	6-month mortality was similar between groups although the difference was statistically significant (0.95% vs. 0.78%; unadjusted RR 1.2, 95% CI 1.1 to 1.4). Definitive conclusions are not possible.†	Insufficient
	Stress echocardiography vs. Nuclear MPI	1 observational (N=212,947 Medicare)	Outpatient	All-cause mortality was similar for stress echocardiography and MPI through 6 months (0.95% vs. 1.28%, adjusted OR 1.00, 95% CI 0.90 to 1.10).	Low
Myocardial Infarction	SPECT vs. Exercise ECG	1 RCT (N=457)	Outpatient	There was low-strength evidence a difference in MI was not found through a mean of 22 months followup (0% vs. 0.5%).	Low
Invasive Coronary Angiography Referral	Exercise ECG vs. Nuclear MPI	1 observational (N=193,406 Medicare)	Outpatient	By 6 months, referral for ICA was less frequent following exercise ECG (9.04% vs. 12.13%, adjusted OR 0.72, 95% CI 0.70 to 0.75).	Low
	Stress echocardiography vs. Exercise ECG	1 observational (n=5894 with no known CAD)	Outpatient	Through a mean of 34 months, ICA referral was similar in patients at low (6% vs. 8%) and intermediate posttest risk (12% vs. 14%) but more frequency in stress echocardiography patients considered to be at high posttest risk (40% vs. 28%, p<0.0001). Definitive conclusions are not possible.†	Insufficient
	Stress echocardiography vs. Exercise ECG	1 observational (N=141,667 Medicare)	Outpatient	Through 6 months, ICA referral was similar although the difference was statistically significant (9.50% vs. 9.04%, unadjusted RR 1.05, 95% CI 1.02 to 1.09). Definitive conclusions are not possible.†	Insufficient

Outcome*	Comparison	Number of Studies (N)	Setting	Conclusions	Strength of Evidence
	Stress echocardiography vs. Nuclear MPI	1 observational (N=212,947 Medicare)	Outpatient	By 6 months, referral for ICA was less frequent following stress echocardiography (9.50% vs. 12.13%; adjusted OR 0.78, 95% CI 0.76 to 0.81).	Low
Revascularization	SPECT vs. Exercise ECG	1 RCT (N=457)	Outpatient	SPECT was associated with fewer revascularizations than exercise ECG (10.8% vs. 17.9%, RD -7.1, 95% CI -13.6 to -0.6 per 100).	Low
	Stress echocardiography vs. Exercise ECG	1 observational (n=5894 with no known CAD)	Outpatient	Through a mean of 34 months, revascularization was performed in a similar percentage of stress echocardiography patients at low (5% vs. 7%) and intermediate posttest risk (8% vs. 9%) but in more stress echocardiography patients considered to be at high posttest risk (29% vs. 20%). Definitive conclusions are not possible.†	Insufficient
	Exercise ECG vs. Nuclear MPI	1 observational (N=193,406 Medicare)	Outpatient	Revascularization through 6 months was similar between groups although the difference was statistically significant (4.31% vs. 4.59%, respectively; adjusted OR 0.90, 95% CI 0.85 to 0.94).	Low
	Stress echocardiography vs. Exercise ECG	1 observational (N=141,667 Medicare)	Outpatient	Through 6 months, the frequency of revascularization was similar between groups (4.22% vs. 4.31%). Definitive conclusions are not possible.†	Insufficient
	Stress echocardiography vs. Nuclear MPI	1 observational (N=212,947 Medicare)	Outpatient	Revascularization through 6 months was similar between groups although the difference was statistically significant (4.22% vs. 4.59%, adjusted OR 0.93, 95% CI 0.88 to 0.98).	Low
Percutaneous Coronary Intervention	Exercise ECG vs. Nuclear MPI	1 observational (N=193,406 Medicare)	Outpatient	Through 6 months, PCI was similar between groups although the difference was statistically meaningful (2.57% vs. 3.37%, adjusted OR 0.72, 95% CI 0.68 to 0.77).	Low
	Stress echocardiography vs. Exercise ECG	1 observational (n=5894 with no known CAD)	Outpatient	Through a mean of 34 months, PCI was performed in a similar percentage of stress echocardiography patients at low (4% vs. 6%) and intermediate posttest risk (5% vs. 6%) but in more stress echocardiography patients considered to be at high posttest risk (22% vs. 12%). Definitive conclusions are not possible.†	Insufficient
	Stress echocardiography vs. Exercise ECG	1 observational (N=141,667 Medicare)	Outpatient	Through 6 months, there was a similar frequency of PCI between groups (2.61% vs. 2.57%). Definitive conclusions are not possible.†	Insufficient

Outcome*	Comparison	Number of Studies (N)	Setting	Conclusions	Strength of Evidence
	Stress echocardiography vs. Nuclear MPI	1 observational (N=212,947 Medicare)	Outpatient	Through 6 months, PCI referral occurred similarly between groups although the difference was statistically significant (2.61% vs. 3.37%, adjusted OR 0.76, 95% CI 0.72 to 0.81).	Low
Coronary Artery Bypass Graft	Exercise ECG vs. Nuclear MPI	1 observational (N=193,406 Medicare)	Outpatient	Through 6 months, CABG was done similarly between groups although the difference was statistically significant (1.82% vs. 1.29%, adjusted OR 1.37, 95% CI 1.26 to 1.49).	Low
	Stress echocardiography vs. Exercise ECG	1 observational (n=5894 with no known CAD)	Outpatient	Through a mean of 34 months, CABG was performed in a similar percentage of stress echocardiography patients at low (1% vs. 2%) and intermediate posttest risk (3% in both groups) but in fewer stress echocardiography patients considered to be at high posttest risk (6% vs. 18%). Definitive conclusions are not possible.†	Insufficient
	Stress echocardiography vs. Exercise ECG	1 observational (N=141,667 Medicare)	Outpatient	CABG was performed similarly between groups through 6 months (1.69% vs. 1.82%). Definitive conclusions are not possible.†	Insufficient
	Stress echocardiography vs. Nuclear MPI	1 observational (N=212,947 Medicare)	Outpatient	Through 6 months, CABG referral occurred similarly between groups although the difference was statistically significant (1.69% vs. 1.29%, adjusted OR 1.40, 95% CI 1.29 to 1.52).	Low
Additional Testing	Exercise echocardiography vs. Exercise ECG	1 RCT (N=111)	Various	Stress echocardiography was associated with significantly less additional testing compared with exercise ECG (3.5% vs. 24.1%; RD=22, 95% CI -34 to -10). Definitive conclusions are not possible.†	Insufficient
	Stress echocardiography vs. Exercise ECG	1 observational (N=141,667 Medicare)	Outpatient	Additional noninvasive testing through 6 months was more common following stress (5.57% vs. 19.34%, unadjusted RR 0.29, 95% CI 0.28 to 0.30); this was driven by significantly fewer referrals for MPI (4.03% vs. 16.47%; unadjusted RR 0.24, 95% CI 0.24 to 0.25). Definitive conclusions are not possible.†	Insufficient
	Stress echocardiography vs. Nuclear MPI	1 observational (N=212,947 Medicare)	Outpatient	Referral for additional testing was somewhat more frequent for stress echocardiography than MPI in the 6 months after initial testing (5.57% vs. 3.22%; adjusted OR 1.92, 95% CI 1.83 to 2.0).	Low

Outcome*	Comparison	Number of Studies (N)	Setting	Conclusions	Strength of Evidence
Hospitalization (Cardiac related)	Exercise ECG vs. Nuclear MPI	1 observational (N=193,406 Medicare)	Outpatient	Similar very low frequency of hospitalization for acute MI through 6 months (0.32% vs. 0.43%). Definitive conclusions are not possible.†	Insufficient
	Stress echo vs. Exercise ECG	1 observational (N=141,667 Medicare)	Outpatient	Similar very low frequency of hospitalization for acute MI through 6 months (0.32% in both groups). Definitive conclusions are not possible.†	Insufficient
	Stress echocardiography vs. Nuclear MPI	1 observational (N=212,947 Medicare)	Outpatient	Hospitalization for acute MI through 6 months was similar between groups although the difference was statistically significant (0.32% vs. 0.43%, adjusted OR 0.83, 95% CI 0.70 to 0.98). Definitive conclusions are not possible.†	Insufficient

CABG = coronary artery bypass graft; CAD = coronary artery disease; CI = confidence interval; ECG = electrocardiography; ICA = invasive coronary angiography; MI = myocardial infarction; MPI = myocardial perfusion imaging; NS = not statistically significant; OR = odds ratio; PCI = percutaneous intervention; RCT = randomized controlled trial; RD = risk difference; SPECT = single photon emission computed tomography.

*Primary outcomes not listed in this table had no evidence and thus insufficient strength of evidence.

†Definitive conclusions are not possible due to study limitations and/or imprecision in observational studies or lack of data in RCTs.

Anatomic Tests Versus Functional Tests

CCTA Versus Exercise ECG

Two fair-quality studies, one RCT⁷⁸ and one retrospective database study,⁹⁶ compared CCTA with exercise ECG in patients with mixed pretest risk (Appendix E, Tables E4–E9, E40, G3).

In the trial, patients with low (43%), intermediate (23%), and high (34%) pretest risk (defined as <30%, 30%–60%, and >60% according to Diamond and Forrester) presented with stable chest pain to two emergency departments (EDs) in Northern Ireland.⁷⁸ Patients were randomized to either 64-slice CCTA with contrast (n=243) or exercise ECG testing using the Bruce protocol (n=245); outcomes were assessed at 3 and 12 months. Both groups were similar in terms of mean age (58 years), presenting symptoms, and all reported cardiac risk factors. However, more women received CCTA compared with exercise ECG (47% vs. 39%). Outcomes were reported at 3 and 12 months; 97.6% of patients completed final followup. This trial received funding from the South Eastern Health and Social Care Trust as well as the Northern Ireland Cardiovascular Network. Methodological shortcoming included no statement of concealed allocation and lack of clear blinding of outcome assessors.

A large administrative database study was conducted using a 20 percent random sample of Medicare claim records from 2006 to 2008 (N=282,830); patients could receive one of four tests including CCTA (n=8820) and exercise ECG (n=61,063) and the followup period was 6 months.⁹⁶ Pretest CAD risk and other baseline risk scores were not reported. Included claims were limited to those in an outpatient setting for patients aged 66 years or older; no patient had a history of known CAD (within the previous 9 months) or prior MI or revascularization (within the previous 12 months). This study was designed to evaluate CCTA, but the data provided allowed some comparisons across the other tests. No test details were reported; to include

information regarding how a test was chosen for a given patient, only CPT (Current Procedural Terminology) codes that included both CCTA and stress (exercise and pharmacological) ECG were provided. Mean age was similar in both group (73 years); a higher percentage of women had undergone CCTA (55.8% vs. 49.0%). Cardiac risk factors were more prevalent in the CCTA as compared with the ECG group: hypertension (65.5% vs. 57.5%), hyperlipidemia (72.1% vs. 65.1%), and diabetes (30.0% vs. 25.0%). This study was funded by the American Heart Association. Methodological limitations included lack of blinded outcomes assessment and significant baseline differences between groups.

Clinical outcomes. In the trial, no difference was found in all-cause mortality between groups through 12 months (0.4% vs. 0.4%); no patients died of cardiac-related events.⁷⁸ Similarly, there was no difference in the incidence of MI (0.41% vs. 0.82%, RD -0.4, 94% CI -1.8 to 1.0 per 100) or acute coronary syndrome (0.41% vs. 1.2%; RD -0.8, 95% CI -2 to 0.8 per 100). Hospitalization for cardiac causes occurred significantly less frequently in the CCTA group (0.8% vs. 6.9%, RD -6.1, 95% CI -9.5 to -2.7 per 100) through 12 months. In the Medicare claims study, 6-month all-cause mortality was similar between groups although the results were statistically significant (1.05% vs. 0.78%; RR 1.3, 95% CI 1.08 to 1.68). Risk of hospitalization for MI was reduced in the CCTA group compared with the exercise ECG group (0.19% vs. 0.32%, unadjusted RR 0.60, 95% CI 0.37 to 0.99).⁹⁶

In the RCT, using the Seattle Angina Questionnaire, quality of life improved slightly more from baseline in the CCTA group versus the exercise ECG group at 3 (difference between groups: -5.7, p=0.014) and 12 months (difference between groups: -4.8; p=0.041). Using the same tool, patient assessment of angina stability was also improved more in the CCTA group at 3 (difference between groups: -11.1; p=0.001) and 12 months (difference between groups: -6.8; p=0.028). Frequency of angina symptoms were similar between groups at both timepoints.⁷⁸

Clinical management. The trial of ED patients reported that through 12 months, CCTA was associated with a greater frequency of ICA referral compared with exercise ECG (27.2% vs. 20.8%, RD 6.3, 95% CI -1.2 to 13.9 per 100, p=0.1011), though the result did not achieve statistical significance.⁷⁸ During this period, more patients underwent revascularization following testing with CCTA compared with exercise ECG (15.2% vs. 7.7%, RD 7.5, 95% CI 1.9 to 13.0 per 100), including PCI (12% vs. 5%, RD 7, 95% CI 2 to 12 per 100); referral for CABG was similar between groups (3.3% vs. 2.9%, RD 0.00, 95% CI -0.03 to 0.04 per 100). CCTA resulted in significantly fewer additional noninvasive cardiac tests through 12 months (2.4% vs. 31.3%, RD -29, 95% CI -37 to -23 per 100). More patients assigned to CCTA received medical therapy (40.7% vs. 14.3%, RD 26, 95% CI 19 to 34 per 100) and fewer received no intervention (44% vs. 78%; RD -0.37, 95% CI -0.45 to -0.29) compared with the exercise ECG group. However, the CCTA group had fewer revisits for chest pain (3.3% vs. 13.1%; RD -0.10, 95% CI -0.15 to -0.05) and fewer days in the hospital for chest pain (mean 7 vs. 56 days) than exercise ECG.

The database study of Medicare outpatients found that CCTA was associated with higher referral rates for ICA through 6 months (22.9% vs. 9.0%, unadjusted RR 2.5, 95% CI 2.4 to 2.7) as well as higher rates of revascularization (11% vs. 4.3%, unadjusted RR 2.65, 95% CI 2.47 to 2.84). Similarly, the study found increased referral for PCI with CCTA compared with exercise ECG through 6 months (7.9% vs. 2.6%, unadjusted RR 3.05, 95% CI 2.80 to 3.33) but there was only a small difference between groups in the risk for CABG (3.7% vs. 1.8%; unadjusted RR 2.04 95% CI 1.80 to 2.30). There was less additional noninvasive testing in CCTA patients through 6 months (5% vs. 19%; unadjusted RR 0.26, 95% CI 0.23 to 0.28); this was driven by a

significantly lower referral rate for MPI (2.7% vs. 16.5%, unadjusted RR 0.17, 95% CI 0.15 to 0.19, respectively).⁹⁶

Harms of index test and consequences of testing. In the RCT of mixed risk-level patients comparing CCTA and exercise ECG testing, there was only a statement of no complications associated with any investigation.⁷⁸

Harms of additional testing. Not reported by either study.

Differential effectiveness or safety in subgroups. No analyses related to differential effectiveness or safety of CCTA versus exercise ECG with regard to patient characteristics or other factors were provided in either study however the database study included only Medicare patients.

CCTA Versus SPECT

Two observational studies, one fair-quality⁹¹ and one poor-quality,⁹⁸ compared CCTA to SPECT but did not report or stratify results by pretest risk of CAD (Appendix E, Tables E7–E9, E40, G3).^{91, 98} Min et al. 2008 compared CCTA (n=1938) to SPECT (n=7752) in an administrative database study using records dated January through March 2006 from a large private United States claims database; SPECT patients were matched to CCTA patients.⁹¹ Pretest CAD risk and other baseline risk scores were not reported. Outcomes were reported at 9 months. Tandon et al. 2012 reported 6-month results from a prospective registry study of 2442 patients (University of Ottawa Heart Institute Cardiac CT Registry); 1221 consecutive CCTA patients were enrolled between 2006 and 2009 and matched to 1221 SPECT patients from the same time period.⁹⁸ Overall, the median pretest CAD risk in this population was 12.3 (scale not reported) and the Morise score was a mean 10.7 ± 3.0 . The number of sites and the setting was not reported in either study; the database study was conducted in the United States and the registry study in Canada. Funding for the database study came from a GE Healthcare grant; the registry study received support from the Ontario Research Fund and the Canada Foundation for Innovation. The database study did not report any test details;⁹¹ the registry study used 64-slice CCTA with contrast and rest-stress SPECT employed exercise or pharmacological stress (percentage of each not reported).⁹⁸ The database study considered patients with no history of CAD recorded in the 9 months prior to testing; the registry study enrolled patients with no history of CAD or revascularization. Except slightly more CCTA patients having baseline dyslipidemia (47.4% vs. 38.7%) in the registry study,⁹¹ CCTA and SPECT groups were comparable in all baseline characteristics reported; this is likely a consequence of the patient-matching process during enrollment. Methodological limitations included lack of blinded outcomes assessment, unclear attrition, and lack of controlling for confounding of baseline differences between groups in dyslipidemia in the registry study.

Clinical outcomes. In the registry study, 0.2 percent of CCTA patients died of cardiac causes during the followup period, but mortality rates in the SPECT group were not reported.⁹⁸ The database study reported similar 9-month risk of MI in both CCTA and SPECT groups (0.4% vs. 0.6%),⁹¹ and the registry study reported MI in 0.5 percent of CCTA patients during 6-month followup but again did not report data for the SPECT group.⁹⁸ The database study found the 9-month risk of hospitalization for cardiovascular causes was similar in the CCTA and SPECT patients (4.2% vs. 4.1%), although the length of stay was significantly shorter in the CCTA group (4.5 ± 4.1 vs. 7.4 ± 13.3 days, mean difference -2.9, 95% CI -3.5 to 2.3).⁹¹ The database study also found no difference between groups in the risk of new-onset angina through 9 months (3.0% vs. 3.5%).⁹¹

Clinical management. The database study reported that fewer CCTA patients underwent ICA within the 9-month followup period compared with SPECT patients (6.2% vs. 9.5%, OR 1.61, 95% CI 1.32 to 1.97),⁹¹ while the registry found no difference between groups (10.6% vs. 10.2%) through 6 months.⁹⁸ In the latter study, however, ICA results showed significantly fewer false positives (i.e., no obstructive CAD) in patients that received CCTA as the index test (9.7% vs. 25.8%). Although there was no difference between CCTA and SPECT groups in the database study in the 9-month risk of additional CCTA testing (0.8% vs. 0.7%), CCTA patients were more likely to undergo additional SPECT (7.5% vs. 1.4%, OR 0.17, 95% CI 0.13 to 0.22).⁹¹ The registry did not report additional noninvasive testing.⁹⁸ Both studies found no difference between CCTA and SPECT groups in the need for subsequent revascularization, including PCI and CABG, during the followup periods.^{91, 98} The database study reported similar CAD-specific medication use between groups; there was also no difference in the percentage of patients who attended cardiovascular outpatient visits during the 9-month followup period.⁹¹

Harms of index test and consequences of testing. Radiation exposure was significantly greater following index CCTA as compared with SPECT in one registry study (median, interquartile range [IQR]): 14.9 (13.1 to 17.1) versus 10.5 (10.1 to 11.4) mSv; $p < 0.001$.⁹⁸

Harms of additional testing. Radiation exposure from subsequent invasive coronary angiography was also significantly greater in patients who underwent CCTA versus SPECT in one registry study (median, IQR): 15.2 (12.7 to 17.1) (n=129) versus 10.8 (10.2 to 11.7) (n=125) mSv; $p < 0.001$.⁹⁸

Differential effectiveness or safety in subgroups. No analyses related to differential effectiveness or safety of CCTA versus SPECT with regard to patient characteristics or other factors were provided in either study.^{91, 98}

CCTA Versus Nuclear MPI

Two fair-quality observational studies compared CCTA to myocardial perfusion imaging (MPI) (SPECT or PET) (Appendix E, Tables E4–E9, E40, G3).^{96, 99} Shreibati et al. conducted a large administrative database study using a 20 percent random sample of Medicare claim records from 2006 to 2008 (N=282,830); patients could receive one of four tests including CCTA (n=8820) and MPI (n=132,343).⁹⁶ The database study was limited to claims in an outpatient setting for patients aged 66 years or older; no patient had a history of known CAD (within the previous 9 months) or prior MI or revascularization (within the previous 12 months). Yamauchi et al. reported data from a prospective observational study conducted across 81 centers in Japan in which patients could receive CCTA (n=635), MPI (n=1221), or ICA (not included in this report); the setting was not reported.⁹⁹ The database study reported 6-month outcomes,⁹⁶ while the prospective study reported outcomes for 96.6% of patients at a median followup of 17.0 ± 5.9 months.⁹⁹ In general, no test details were reported in either study. Both studies employed myocardial perfusion imaging; Shreibati et al. specified a number of CPT (Current Procedural Terminology) codes that included both SPECT and PET.⁹⁶ Yamauchi et al. did not indicate which types of imaging constituted MPI⁹⁹ and an assumption was made by the authors of this report that both SPECT and PET were likely to have been used. No information was provided regarding how a test was chosen for a given patient in the database study;⁹⁶ in the prospective nonrandomized study the test was selected at the discretion of the physician.⁹⁹ In the database study, CCTA patients were slightly younger than MPI patients (mean age 73.56 vs. 75.71 years, $p < 0.001$) and had fewer risk factors and comorbidities; outcomes were adjusted for confounding baseline variables. Females comprised 54.6% of the population, and pretest CAD risk (or other

baseline risk score) was not reported.⁹⁶ Those in the prospective nonrandomized study population had a mean age of 66 years, and 44.5 percent were female; patients tested with CCTA group were less likely than those who received MPI to have milder symptoms (New York Heart Association class I [80.6% vs. 91.9%]; and Canadian Cardiovascular Society class I [61.8% vs. 77.9%]).⁹⁹ The database study was funded by the American Heart Association and the prospective observational study did not report its source of funding. Methodological limitations included lack of blinded outcomes assessment, significant baseline differences between groups.

Clinical outcomes. In the database study, the 6-month risk of death from any cause was similar between CCTA and MPI groups (1.05% vs. 1.28%, adjusted OR 1.11, 95% CI 0.88 to 1.38). The same study reported a slightly lower 6-month risk of acute MI hospitalization in the CCTA group (0.19% vs. 0.43%, adjusted OR 0.60, 95% CI 0.37 to 0.98).⁹⁶ The prospective observational study found no difference between CCTA and MPI groups in the median 17-month risk of the composite MACE (death, acute MI, major cardiac event, late (>3 months) revascularization) (2.1% vs. 2.6%, crude RR 0.81, 95% CI 0.43 to 1.53).⁹⁹ Clinical outcomes for test-positive versus test-negative patients were not reported.

Clinical management. While the database study reported higher 6-month ICA referral rates following CCTA compared with MPI (22.94% vs. 12.13%, adjusted OR 2.19, 95% CI 2.08 to 2.32 [MPI as reference group]),⁹⁶ the prospective observational study found no difference between the two groups through a median of 17-month followup (31% vs. 33%).⁹⁹ In the database study, any additional noninvasive testing through 6 months was more common in CCTA than MPI patients (4.98% vs. 3.22%, adjusted OR 1.52, 95% CI 1.37 to 1.69, MPI as reference group); this difference was statistically significant for all types of noninvasive tests employed (MPI, stress echocardiography, exercise ECG) except CCTA.⁹⁶ The prospective observational study reported similar trends, with any additional test (including ICA) being performed in more CCTA than MPI patients (40% vs. 35%, crude RR 1.14, 95% CI 1.01 to 1.29) through a median of 17-month followup.⁹⁹ The database study found that the need for any revascularization was higher in CCTA patients (11.41% vs. 4.59%, adjusted OR 2.76, 95% CI 2.56 to 2.98 [MPI as reference group]) through 6 months; this trend held true for both PCI (7.85% vs. 3.37%, adjusted OR 2.49, 95% CI 2.28 to 2.72) and CABG (3.71% vs. 1.29%, adjusted OR 3.00, 95% CI 2.63 to 3.42 [MPI as reference group]).⁹⁶ In the database study, not only did more CCTA patients undergo ICA, they were more likely to receive revascularization following ICA than MPI patients (48.79% vs. 37.53%, adjusted OR 1.56, 95% CI 1.41 to 1.73 [MPI as reference group], $p < 0.001$).⁹⁶ The prospective observational study similarly reported a higher risk of any revascularization in the CCTA group (%'s not reported, adjusted OR 1.62, 95% CI 1.20 to 2.18) through a median of 17 months followup.⁹⁹

Harms of index test. There was no difference in the risk of adverse events during the test between CCTA and MPI patients (0.5% vs. 0.9%) as reported by one observational study;⁹⁹ no additional details were provided.

Harms of additional testing. No harms of additional testing were reported in either of the two studies.

Differential effectiveness or safety in subgroups. Although no formal test for interaction was performed, the database study⁹⁶ found that the unadjusted 6-month risk of catheterization and revascularization (evaluated separately) were significantly higher in CCTA patients than MPI patients across all subgroups tested, including age (stratified into four groups: 66-69 years, 70-74 years, 75-79 years, and 80-84 years), sex, race (African-American, Caucasian), hypertension, hyperlipidemia, diabetes, tobacco use, Medicaid, year of index test, and referral region.

CCTA Versus Stress Echocardiography

One large, fair-quality administrative database study was identified (Appendix E, Tables E4–E9, E40, G3). This study analyzed a 20 percent random sample of Medicare claim records from 2006 to 2008 (N=282,830); patients could receive one of four tests including CCTA (n=8820) and stress echocardiography (n=80,604) and the followup period was 6 months.⁹⁶ Pretest CAD risk and other baseline risk scores were not reported. Included claims were limited to those in an outpatient setting for patients aged 66 years or older. No patient had a history of known CAD (within the previous 9 months) or prior MI or revascularization (within the previous 12 months). No test details were reported, to include information regarding how a test was chosen for a given patient; only CPT (Current Procedural Terminology) codes that included both CCTA and stress echocardiography were provided. Mean age was similar in both groups (74 years) as was sex (CCTA 56% vs. echocardiography 58% female). Cardiac risk factors were more prevalent in the CCTA as compared with the echocardiography group: hypertension (65.5% vs. 60.2%), hyperlipidemia (72.1% vs. 64.6%), and diabetes (29.9% vs. 26.4%). This study was funded by the American Heart Association. Methodological limitations included lack of blinded outcomes assessment and significant baseline differences between groups.

Clinical outcomes. The 6-month risk of death from any cause was similar between CCTA and stress echocardiography (1.05% vs. 0.95%, unadjusted RR 1.11, 95% CI 0.90 to 1.38) as was the risk of hospitalization for acute MI (0.19% vs. 0.32%, unadjusted RR 0.61, 95% CI 0.37 to 1.00). Clinical outcomes for test-positive versus test-negative patients were not reported.

Clinical management. Significantly higher 6-month ICA referral rates were reported following CCTA compared with stress echocardiography (22.94% vs. 9.50%, unadjusted RR 2.41, 95% CI 2.31 to 2.52). Any additional noninvasive testing through 6 months was similar between groups, respectively (4.98% vs. 5.57%, unadjusted RR 0.89, 95% CI 0.81 to 0.98), but statistically meaningful; this held true for all types of noninvasive tests employed (CCTA, MPI, stress echocardiography, exercise ECG). The need for any revascularization through 6 months was significantly greater following CCTA compared with echocardiography (11.41% vs. 4.22%, respectively; unadjusted RR 2.70, 95% CI 2.53 to 2.89); this trend held true for both PCI (7.85% vs. 2.61%, unadjusted RR 3.01, 95% CI 2.77 to 3.27) and CABG (3.71% vs. 1.69%, unadjusted RR 2.19, 95% CI 1.94 to 2.47). Not only were patients who received CCTA significantly more likely to undergo ICA, they also slightly more likely to receive revascularization following ICA compared with exercise ECG patients (48.79% vs. 43.65%, unadjusted RR 1.12, 95% CI 1.06 to 1.18).

Harms of index test and consequences of testing and harms of additional testing. No harms related to either the index or additional testing were reported.

Differential effectiveness or safety in subgroups. No analyses related to differential effectiveness or safety of nuclear MPI and exercise ECG with regard to patient characteristics or other factors were provided; however the database study focused on Medicare beneficiaries (age \geq 66 years).

Noncomparative Studies: Anatomical

Calcium scoring. One noncomparative study of calcium scoring in patients with an unclear pretest risk reported on predictive accuracy.¹¹⁷ Calcium scoring was performed via nonenhanced electron beam computed tomography; a score of \geq 1.4 was considered a positive test result and a score of $<$ 1.4 was considered a negative test result. A total of 255 patients were analyzed with a mean age of 58 ± 11 years; the proportion of males and females and relevant cardiac risk factors

were not reported. Over a mean followup period of 42 months, the frequency of major adverse cardiac events was significantly higher in those who had a positive compared with a negative result: 20 versus 2 per 100 people (Appendix F, Tables F19–F20).

Two additional studies were identified in our patient population that reported incidental findings at the time of index testing. One study reported incidental findings in 80 (7.8%) of the 1031 patients who underwent calcium scoring via multidetector CT at the time of SPECT in a single emergency department.⁹² Findings included pulmonary nodules or mediastinal/hilar calcifications (n=11), pleural effusions or pulmonary infiltrates (n=7), dilated aorta (n=28), pericardial thickening or effusion (n=16), hiatal hernia (n=7), liver cysts (n=2), valvular calcifications (n=8), and abnormal venous anatomy (n=1). No information was provided about subsequent treatment. In the second study, major noncardiac abnormal findings on CCTA (plus calcium scoring) included pulmonary embolism (n=86), acute aortic syndromes (n=13), malignancy (n=6), pneumonia (n=35), advanced emphysema (n=1), and large pericardial (n=15) or pleural (n=22) effusion; these patients were subsequently excluded from analysis due to concerns regarding the effect on immediate patient care or short- or long-term prognosis.⁹³ Nonacute findings (e.g., lung nodules <8 mm, subsegmental atelectasis, bronchial wall thickening, or hiatal hernia) did not preclude exclusion in the study; however, the authors did not report if or how many of these findings were presents in their population (N=458).

Noncomparative Studies: Functional

Stress echocardiography. Two noncomparative studies of stress echocardiography in patients with unknown pretest risk reported on predictive accuracy. Both studies were conducted in an outpatient setting and employed treadmill exercise stress. One study enrolled a high number of patients with known CAD but only the outcomes for the subgroup of patients without known CAD are presented here (n=211).¹¹³ The second study enrolled only women and 18 percent of the population had known CAD (N=405).¹⁰⁹ Mean ages were 62 and 56 years. Cardiac risk factors were reported variably across studies. In the study conducted in women only, the frequency of any cardiac events was 31 versus 4 per 100 people over a mean of 41 months (OR 9.8, 95% CI 4.4 to 21.9; and for cardiac death: OR 13.6, 95% CI 4.5 to 42). In the second study, the frequency of any cardiac event and myocardial infarction at 12 months was 32 versus 7 per 100 people and 9 versus 1 per 100 people, respectively; there were no deaths reported in either group (Appendix F, Tables F15–F18).

Stress ECG. Two noncomparative studies of stress ECG in patients with unknown pretest risk reported on predictive accuracy. One study (N=132) was conducted in elderly patients (mean age 71 years) hospitalized for cardiac events associated with suspected CAD and utilized bicycle exercise or dipyridamole stress.¹⁰⁷ The second study was conducted in an outpatient setting, enrolled women only (mean age 56 years), and employed treadmill exercise (N=405).¹⁰⁹ The latter study also excluded patients with early revascularization to control for test-driven events. In the study that enrolled women only, a positive test, as compared with a negative test, was associated with a significantly greater risk of any cardiac event over a mean 41 months followup (15 vs. 5 per 100 people; OR 3.1, 95% CI 1.2 to 7.9) but not with the risk of cardiac-related death (OR 1.6; 95% CI 0.3 to 8.8). In the study enrolling only elderly patients, the frequency of any cardiac event was higher in test-positive as compared with test-negative patients (40 vs. 22 per 100 people); the rate in the positive group was driven by a high occurrence of hospitalization for revascularization. Conversely, the frequency of reported MI was less in those with positive

results (3 vs. 14 per 100 people) and frequency of mortality was the same between groups (7 per 100 people) (Appendix F, Tables F17–F18).

Table 14. Summary of findings and strength of evidence: Mixed pretest risk – anatomical versus functional testing

Outcome*	Comparison	Number of Studies (N)	Setting	Conclusions	Strength of Evidence
Mortality (all-cause)	CCTA vs. Exercise ECG	1 RCT (N=500)	ED	There is low strength of evidence that no difference was found in all-cause mortality between groups through 12 months (0.4% in both groups).	Low
	CCTA vs. Exercise ECG	1 observational (N=69,883 Medicare)	Outpatient	Through 6 months, mortality was similar between groups although the results were statistically significant (1.05% vs. 0.78%, unadjusted RR 1.3, 95% CI 1.08 to 1.68). Definitive conclusions are not possible.†	Insufficient
	CCTA vs. SPECT	1 observational (N=9690)	NR	The 9-month risk of MI was similar in both groups (0.4% vs. 0.6%). Definitive conclusions are not possible.†	Insufficient
	CCTA vs. Nuclear MPI	1 observational (N=141,163 Medicare)	Outpatient	No difference between groups through 6 months (1.05% vs. 1.28%, adjusted OR 1.11, 95% CI 0.88 to 1.38).	Low
	CCTA vs. Stress echocardiography	1 observational (N=89,424 Medicare)	Outpatient	6-month mortality was similar between groups (0.95% vs. 1.05%, unadjusted RR 1.1 95% CI 0.9 to 1.4). Definitive conclusions are not possible.†	Insufficient
Myocardial Infarction	CCTA vs. Exercise ECG	1 RCT (N=500)	ED	There is low strength of evidence that no difference was found through 12 months in the incidence of MI between groups (0.41% vs. 0.82%, RD -0.4, 94% CI -1.8 to 1.0 per 100).	Low
Invasive Coronary Angiography Referral	CCTA vs. Exercise ECG	1 RCT (N=500)	ED	CCTA was associated with higher referral rates for ICA through 12 months (27.2% vs. 20.8%; RD 6.3, 95% CI -1.2 to 13.9 per 100 p=0.1011).	Low
	CCTA vs. Exercise ECG	1 observational (N=69,883 Medicare)	Outpatient	CCTA was associated with higher referral rates for ICA through 6 months (22.9% vs. 9.0%, unadjusted RR 2.5, 95% CI 2.4 to 2.7). Definitive conclusions are not possible.†	Insufficient
	CCTA vs. SPECT	2 observational (N=12,132)	NR	Results were inconsistent between studies, with one reporting that ICA was less common in CCTA patients through 9 months (6.2% vs. 9.5%, OR 1.61, 95% CI 1.32 to 1.97), while the other study found no difference between groups (10.6% vs. 10.2%) through 6 months. Definitive conclusions are not possible.†	Insufficient
	CCTA vs. Nuclear MPI	1 observational (N=1856)	NR	Groups were similar regarding ICA referral through a median of 1.42 years followup (31% vs. 33%). Definitive conclusions are not possible.†	Insufficient
	CCTA vs. Nuclear MPI	1 observational (N=141,163 Medicare)	Outpatient	Higher 6-month ICA referral following CCTA compared with MPI was reported (22.94% vs. 12.13%, adjusted OR 2.19, 95% CI 2.08 to 2.32).	Low

Outcome*	Comparison	Number of Studies (N)	Setting	Conclusions	Strength of Evidence
	CCTA vs. Stress echocardiography	1 observational (N=89,424 Medicare)	Outpatient	ICA was more common following CCTA through 6 months (22.9% vs. 9.5%, unadjusted RR 2.4, 95% CI 2.3 to 2.5). Definitive conclusions are not possible.†	Insufficient
Revascularization	CCTA vs. Exercise ECG	1 RCT (N=500)	ED	Through 12 months there was greater risk of revascularization with CCTA compared with exercise ECG (15.2% vs. 7.7%, RD 7.5, 95% CI 1.9 to 13.0 per 100).	Low
	CCTA vs. Exercise ECG	1 observational (N=69,883 Medicare)	Outpatient	CCTA was associated more revascularization procedures through 6 months (11% vs. 4.3%, unadjusted RR 2.65, 95% CI 2.47 to 2.84). Definitive conclusions are not possible.†	Insufficient
	CCTA vs. SPECT	2 observational (N=12,132)	NR	CCTA and SPECT groups were similar regarding subsequent revascularization (2.1% to 6.2% vs. 1.6% to 5.9%) during 6 to 9 months followup. Definitive conclusions are not possible.†	Insufficient
	CCTA vs. Nuclear MPI	1 observational (N=1856)	NR	Revascularization was more common following CCTA than SPECT through a median of 1.42 years (% NR, adjusted OR 1.62, 95% CI 1.20 to 2.18).	Low
	CCTA vs. Nuclear MPI	1 observational (N=141,163 Medicare)	Outpatient	Revascularization was higher in CCTA than MPI at 6 months (11.41% vs. 4.59%, adjusted OR 2.76, 95% CI 2.56 to 2.98).	Low
	CCTA vs. Stress echocardiography	1 observational (N=89,424 Medicare)	Outpatient	Revascularization was more common in the 6 months following CCTA compared with stress echocardiography (11.4% vs. 4.2%, unadjusted RR 2.7, 95% CI 2.5 to 2.9). Definitive conclusions are not possible.†	Insufficient
Percutaneous Coronary Intervention	CCTA vs. Exercise ECG	1 RCT (N=500)	ED	CCTA was associated with a significantly higher risk of PCI through 12 months (11.9% vs. 4.9%, RD 7, 95% CI 2 to 12 per 100).	Low
	CCTA vs. Exercise ECG	1 observational (N=69,883 Medicare)	Outpatient	Through 6 months, CCTA patients had more PCI procedures (7.9% vs. 2.6%, unadjusted RR 3.05, 95% CI 2.80 to 3.33). Definitive conclusions are not possible.†	Insufficient
	CCTA vs. SPECT	2 observational (N=12,132)	NR	Both studies found no difference between CCTA and SPECT groups in the frequency of PCI (0.1% to 3.9% vs. 0.1% to 4.0%) during 6 to 9 months followup. Definitive conclusions are not possible.†	Insufficient
	CCTA vs. Nuclear MPI	1 observational (N=141,163 Medicare)	Outpatient	PCI rates were higher in CCTA patients through 6 months followup (7.85% vs. 3.37%, adjusted OR 2.49, 95% CI 2.28 to 2.72).	Low

Outcome*	Comparison	Number of Studies (N)	Setting	Conclusions	Strength of Evidence
	CCTA vs. Stress echocardiography	1 observational (N=89,424 Medicare)	Outpatient	By 6 months, PCI was more common in the CCTA group (7.85% vs. 2.61%, unadjusted RR 3.01 95% CI 2.77 to 3.27). Definitive conclusions are not possible. [†]	Insufficient
Coronary Artery Bypass Graft	CCTA vs. Exercise ECG	1 RCT (N=500)	ED	Through 12 months, there was no difference between groups in CABG (3.3% vs. 2.9%, RD 0.00, 95% CI -0.03 to 0.04 per 100).	Low
	CCTA vs. Exercise ECG	1 observational (N=69,883 Medicare)	Outpatient	There was only a small difference between groups in the risk for CABG through 6 months (3.7% vs. 1.8%; unadjusted RR 2.04 95% CI 1.80 to 2.30). Definitive conclusions are not possible. [†]	Insufficient
	CCTA vs. SPECT	2 observational (N=12,132)	NR	Both studies found no difference between CCTA and SPECT groups in the need for CABG (0.7% to 2.3% vs. 0.5% to 1.9%) during 6 to 9 months followup. Definitive conclusions are not possible. [†]	Insufficient
	CCTA vs. Nuclear MPI	1 observational (N=141,163 Medicare)	Outpatient	CABG was more common in CCTA patients through 6 months followup (3.71% vs. 1.29%, adjusted OR 3.00, 95% CI 2.63 to 3.42).	Low
	CCTA vs. Stress echocardiography	1 observational (N=89,424 Medicare)	Outpatient	By 6 months, CABG had been performed somewhat more frequently in the CCTA group (3.71% vs. 1.69%, unadjusted RR 2.19, 95% CI 1.94 to 2.47). Definitive conclusions are not possible. [†]	Insufficient
Additional Testing	CCTA vs. Exercise ECG	1 RCT (N=500)	ED	CCTA resulted in fewer additional noninvasive cardiac tests through 12 months (2.4% vs. 31.3%, RD -29, 95% CI -37 to -23 per 100).	Moderate
	CCTA vs. Exercise ECG	1 observational (N=69,883 Medicare)	Outpatient	There was less additional noninvasive testing in CCTA patients through 6 months (5% vs. 19%; unadjusted RR 0.26, 95% CI 0.23 to 0.28). Definitive conclusions are not possible. [†]	Insufficient
	CCTA vs. SPECT	2 observational (N=12,132)	NR	Results were inconsistent between studies, with one study showing no difference between groups in the 9-month risk of additional testing (0.8% vs. 0.7%), and the other study showing that CCTA patients were more likely to undergo additional testing through 6 months (7.5% vs. 1.4%, OR 0.17, 95% CI 0.13 to 0.22). Definitive conclusions are not possible. [†]	Insufficient
	CCTA vs. Nuclear MPI	1 observational (N=141,163 Medicare)	Outpatient	Any additional noninvasive testing through 6 months was more common in CCTA than MPI patients (4.98% vs. 3.22%, adjusted OR 1.52, 95% CI 1.37 to 1.69).	Low

Outcome*	Comparison	Number of Studies (N)	Setting	Conclusions	Strength of Evidence
	CCTA vs. Stress echocardiography	1 observational (N=89,424 Medicare)	Outpatient	Additional noninvasive testing through 6 months was similar between groups, although the difference was statistically significant (4.98% vs. 5.57%, unadjusted RR 0.89, 95% CI 0.81 to 0.98). Definitive conclusions are not possible.†	Insufficient
Hospitalization (Cardiac related)	CCTA vs. Exercise ECG	1 RCT (N=500)	ED	Hospitalization for cardiac causes occurred less frequently in the CCTA group (0.8% vs. 6.9%, RD -6.1, 95% CI -9.5 to -2.7 per 100) through 12 months.	Moderate
	CCTA vs. Exercise ECG	1 observational (N=69,883 Medicare)	Outpatient	Through 6 months, hospitalization for acute MI occurred similarly across groups although the results were statistically significant (0.19% vs. 0.32%, unadjusted RR 0.60, 95% CI 0.37 to 0.99). Definitive conclusions are not possible.†	Insufficient
	CCTA vs. SPECT	1 observational (N=9690)	NR	The 9-month rate of hospitalization for cardiovascular causes was similar in the CCTA and SPECT patients (4.2% vs. 4.1%). Definitive conclusions are not possible.†	Insufficient
	CCTA vs. Nuclear MPI	1 observational (N=141,163 Medicare)	Outpatient	Hospitalization for acute MI through 6 months was similar between groups, though the results were statistically significant (0.19% vs. 0.43%, adjusted OR 0.60, 95% CI 0.37 to 0.98). Definitive conclusions are not possible.†	Insufficient
	CCTA vs. Stress echocardiography	1 observational (N=89,424 Medicare)	Outpatient	Through 6 months, hospitalization for acute MI slightly was similar between groups (0.19% vs. 0.32%, unadjusted RR 0.61, 95% CI 0.37 to 1.0). Definitive conclusions are not possible.†	Insufficient
Harms of Index Test	CCTA vs. Exercise ECG	1 RCT (N=500)	ED	There were no complications associated with either test (specifics not reported). Definitive conclusions are not possible.†	Insufficient
	CCTA vs. Nuclear MPI	1 observational (N=1856)	NR	There was no difference in the risk of adverse events during the test between CCTA and MPI patients (0.5% vs. 0.9%); no other details were reported. Definitive conclusions are not possible.†	Insufficient

CABG = coronary artery bypass graft; CAD = coronary artery disease; CCTA = coronary computed tomography angiography; CI = confidence interval; ECG = electrocardiography; ED = emergency department; ICA = invasive coronary angiography; MI = myocardial infarction; MPI = myocardial perfusion imaging; NS = not statistically significant; OR = odds ratio; PCI = percutaneous intervention; RCT = randomized controlled trial; RD = risk difference; RR = relative risk; SPECT = single photon emission computed tomography.

*Primary outcomes not listed in this table had no evidence and thus insufficient strength of evidence.

†Definitive conclusions are not possible due to study limitations and/or imprecision in observational studies or lack of data in RCTs.

Discussion

Key Findings and Strength of Evidence

Evidence to determine the comparative effectiveness and safety of different noninvasive testing strategies for coronary artery disease (CAD) is limited. While there is a robust body of literature on the diagnostic performance of these tests based on traditional measures of test accuracy (e.g., sensitivity, specificity), only a small number of studies were identified that evaluated the impact of noninvasive testing on clinical outcomes measures in the population of interest for this report. The key findings and strength of evidence for the outcomes identified as being most clinically important are summarized in Tables 7–14 in the Results section; factors used to determine the overall strength of evidence are summarized in Appendix J.

A total of 22 comparative studies that evaluated the impact of noninvasive testing on clinical outcomes and/or clinical management outcomes in the population of interest for this report form the basis of this review, including 13 randomized controlled trials (RCTs) (2 good quality, 8 fair quality and 3 poor quality),⁷¹⁻⁸³ nine comparative observational studies (6 fair quality, 3 poor quality).^{84, 86-91, 94, 96, 98, 99} Common methodological shortcomings in the RCTs included unclear description of randomization sequence and/or test allocation and lack of blinded outcomes assessment. In the observational studies, lack of controlling for confounding and/or blinding of outcomes assessment were common methodological shortcomings. The comparative studies served as the basis of the report and were stratified based on pretest risk, test type (anatomic or functional), and setting. For most outcomes reported in trials, the strength of evidence was rated as low (meaning that our confidence in the estimates of effect is low) based on concerns related to precision and study limitations. However, there were some outcomes reported by trials for which the strength of evidence was found to be moderate or high. For the majority of outcomes reported by comparative observational studies, the strength of evidence was found to be insufficient due to study limitations, although some outcomes were graded as low strength of evidence when the estimates were considered to be at low risk for imprecision and confounding was controlled. Eight RCTs and one observational study were conducted in emergency department (ED) settings or specialized chest pain clinics⁷⁸ and compared coronary computed tomography (CCTA) with functional testing^{73-75, 78} or usual care.^{71, 76, 77, 79, 86, 88} In these studies, most of the available data was reported for the index ED visit, and with the exception of two trials reporting 12 month followup, the maximum followup in ED studies was 6 months. The remaining five trials^{72, 80-83} and 13 comparative observational studies were conducted in outpatient, various, or unspecified settings; in general, these studies had longer followup periods, which ranged from a mean of 55 days to 30 months. Pretest risk could not be standardized across studies and was variably determined and defined across studies. Thus, categories of pretest risk below are based on how authors defined it.

Clinical Outcomes

There was no clear difference in myocardial infarction (MI) or all-cause mortality between different testing strategies across settings and pretest risk groups that included intermediate pretest risk patients based on low to moderate strength of evidence from eight trials. The definition of intermediate pretest risk was broad. The frequency of all-cause mortality was low across studies in all settings. In trials enrolling outpatients, all-cause mortality frequency ranged from 0 to 1.5 percent for a variety of noninvasive testing strategies and the frequency in trials in

the ED setting past the initial index visit ranged from 0 to 1.08 percent, across a variety of noninvasive testing or usual care strategies with no statistical difference between any groups. Similarly the frequency of MI was low ranging from 0 to 0.8 percent in outpatient (up to median of 25 months) studies and 0 to 3 percent (up to 12 months) in ED settings with no statistical differences between groups. The strongest evidence came from three trials, one that compared CCTA with functional testing in an outpatient setting,⁷² and two that compared CCTA with single photon emission computed tomography (SPECT) in an ED setting.^{73, 74} For the trial of CCTA versus functional testing, which was also the largest trial (N =10,003), there were no differences in all-cause mortality between groups through 12 months (0.42% vs. 0.64%) or at median of 25 months (1.48% vs. 1.50%) followup or in nonfatal MI at 12 months (0.36% vs. 0.54%, risk difference [RD] -0.18, 95% confidence interval [CI] -0.44 to 0.08 per 100 people) or median of 25 months (0.60% vs. 0.80%, RD -0.20, 95% CI -0.53 to 0.13 per 100 people)⁷²; strength of was moderate for both outcomes. Across the two trials comparing CCTA with SPECT in an ED setting, there was low strength of evidence that no difference was found between tests for mortality or MI; there were no deaths or MIs reported through a mean of 6 months past the initial ED visit.^{73, 74} Across the remaining trials, the strength of evidence was also low that no difference was found between tests due to lack of precision and study limitations. Higher-quality observational studies (i.e., those that controlled for confounding) supported these findings. No conclusions can be drawn regarding the impact of testing on clinical outcomes for patients at low risk or high risk (without ECG changes or troponin elevation or other characteristics of acute coronary syndrome [ACS]) as only subanalyses of less than 100 patients were available.

Several factors may contribute to finding no statistical differences between tests on clinical outcomes. Given the low incidence of mortality and MI in the across studies noted above, sample sizes in even the largest trials may have been too small to detect differences between tests. The low incidence suggests that study populations may generally have been at the lower end of the intermediate pretest risk range. Improvements in medical therapy in the past few decades, including use of statins, may contribute to the low incidence of these outcomes. An additional consideration is the possibility that differences in the true sensitivity between tests to detect treatable CAD or ability to identify high-risk disease are not large. Small differences in sensitivity may have little impact on the probability of disease when the pretest probability is low. Even if two tests do not have the same sensitivity, the lack of difference in the occurrence of outcome events in most studies between persons who were assigned to receive different tests could be due to either the lack of efficacy of treatments administered to test-positive persons; or the lack of difference in the receipt of effective treatments between test-positive and test-negative persons. Given that studies do not present data on treatments administered to individual study participants (or how testing directed those decisions), we cannot distinguish between these alternatives. Furthermore, information on posttest risk stratification or treatment based on such stratification was not reported in most studies. Information on clinical decisions and outcomes based on whether tests were positive, negative or indeterminate was not described in most comparative studies. It is possible that over- or under-treatment may contribute to similarity in clinical findings. Length of followup may also impact the findings of no difference in clinical outcomes. Two larger trials in outpatient settings (SPECT vs. stress electrocardiography [ECG]⁸³ and CCTA vs. functional testing⁷²) followed patients for two or more years. Most studies in the ED setting did not provide data beyond 6 months of the ED visit; testing is only able to affect

clinical events after the index visit, consequently there is insufficient evidence to draw conclusions regarding clinical outcomes longer term.

Referral for Invasive Coronary Angiography

There was some variability in conclusions regarding invasive coronary angiography (ICA) referral following noninvasive testing. In most studies, ICA was most common following CCTA compared with various functional tests. The strongest evidence came from one good quality trial that compared CCTA with functional testing in outpatients, which found that ICA was significantly more common in the CCTA group than the functional testing group by 90 days (12.19% vs. 8.11%, RD 4.08, 95% CI 2.90 to 5.26 per 100 people) (high strength of evidence). Interestingly, fewer catheterizations in the CCTA group showed no obstructive CAD (3.4% vs. 4.3%),⁷² perhaps due to a lower false positive rate with CCTA. Otherwise, the strength of the quality of evidence regarding ICA referral was low across the remaining trials. Two fair quality trials comparing CCTA with exercise ECG suggest that ICA referral is more common following CCTA up to 12 months following initial ED visit with RD 4.8 (95% CI 0.8 to 8.9 per 100 people) in one trial of low to intermediate risk patients and RD 6.3 (95% CI -1.2 to 13.9 per 100 people) in the other trial of mixed risk; statistical significance was not reached and strength of evidence was low due to study limitations and lack of precision. A large administrative data study in Medicare patients also found that ICA was significantly more common following CCTA compared with nuclear myocardial perfusion imaging (MPI) (22.94% vs. 12.13%, adjusted odds ratio [OR] 2.19, 95% CI 2.08 to 2.32); the strength of evidence was low.⁹⁶ In contrast, across studies comparing CCTA with usual care but there were no statistical difference between testing strategies in any of the trials regardless of pretest risk or setting, however, in the small high risk group from one trial, fewer CCTA patients had ICA at the index visit (RD -18, 95% CI -37 to 0.8, $p=0.0714$); strength of evidence was low. Evidence from observational studies for comparisons of CCTA with other tests was considered insufficient due to study limitations and lack of precision. Regarding comparisons of functional tests, two RCTs^{81, 83} and one large administrative database study⁹⁶ provided low strength of evidence on ICA referral in outpatient settings. One trial comparing SPECT with exercise ECG in intermediate risk women reported a six percent referral for ICA in each test group by 24 months. However, the other trial making this comparison reported significantly a lower frequency of ICA referral following SPECT in a subgroup of intermediate pretest risk patients (RD -32, 95% CI -43 to -22 per 100 people) as well as in a subgroup of high risk patients (RD -41, 95% CI -58 to -24 per 100 people) by 22 months.⁸¹ This same trial used Bayesian methods to model posttest risk and reported that 86 percent of those with low pretest risk finished with low posttest risk and that those with a normal or low risk test in either arm did not receive ICA; 3 percent and 38 percent in the intermediate and high posttest risk groups had ICA following SPECT compared with 13 percent and 85 percent in these respective groups following exercise ECG. As such modeling is not a standard approach to posttest risk assessment, the generalizability of these results is not clear. The administrative database study of Medicare patients reported that compared with nuclear MPI, ICA referral was lower following exercise ECG (OR 0.72, 95% CI 0.70 to 0.75) and stress echocardiography (OR 0.78, 95% CI 0.76 to 0.81)⁹⁶ (low strength of evidence). Evidence from the remaining observational studies was considered insufficient.

None of the studies provided analysis or explicit information regarding unnecessary treatment or testing.

Revascularization

Findings were inconsistent across diagnostic strategies with regard to revascularization referral. There was high strength of evidence from one large trial that any revascularization was more common following CCTA compared with functional testing within 90 days (RD 3.07, 95% CI 2.24 to 3.90 per 100 patients); the same was true for percutaneous coronary intervention (PCI) specifically (RD 2.4, 95% CI 1.7 to 3.1 per 100 patients)⁷² (high strength of evidence). Revascularization was also more common 6 to 12 months following CCTA compared with exercise ECG across two studies (1 RCT, 1 observational)^{78, 96} of mixed risk ED patients (low strength of evidence), as well as across two observational studies comparing CCTA with nuclear MPI^{96, 99} in outpatient setting up to 1.4 years (low strength of evidence). By contrast, revascularization was similar for CCTA and SPECT (pooled RD 2 per 100, 95% CI 0 to 4 per 100 patients) at the index ED visit and at 6 months (pooled RD 0, 95% CI 0 to 1 per 100 patients) across two trials (moderate strength of evidence).^{73, 74} PCI and coronary artery bypass graft (CABG) frequencies these trials were also similar between tests; strength of evidence was moderate. Further, there was low strength of evidence of no statistical differences in revascularization frequency between CCTA and usual care at the index visit or at 1 to 3 months followup based on data from four trials.^{71, 76, 77, 79} Evidence comparing functional tests was inconsistent, with one small trial reporting fewer revascularizations following SPECT than exercise ECG (RD -7.1, 95% CI -13.6 to -0.6 per 100)⁸¹ (low strength of evidence), and one large Medicare administrative database study reporting a similar frequency of revascularization (including PCI and CABG) for exercise ECG (4.31%, vs. 4.59%) and stress echocardiography (4.22% vs. 4.59) compared with nuclear MPI (low strength of evidence). For the latter study, although the difference between groups were statistically significant for both comparators, they may not be clinically significant. Studies did not describe posttest reclassification of risk or decisionmaking for treatment.

Additional Noninvasive Testing

Additional noninvasive testing, which impacts the cost and efficiency of care, was common in most studies. In the ED setting, there was high strength of evidence from two trials of low to intermediate risk patients that additional noninvasive testing was significantly more common following CCTA compared with SPECT at the index visit (RD for largest trial 9.4, 95% CI 6.1 to 12.7 per 100 patients).^{73, 74} In the same setting, there was moderately strong evidence that CCTA was associated with less frequent noninvasive testing compared with usual care at the index visit in one trial⁷⁷ and compared with exercise ECG through 12 months (past the index ED visit)⁷⁸ in another trial. In intermediate risk patients additional testing frequency following CCTA was similar to usual care up to 1 month past ED visit in one trial (low strength of evidence), possibly because many in the usual care group also received noninvasive imaging.⁷⁶ In outpatient settings, the strength of evidence was moderate that SPECT was associated with significantly less additional noninvasive testing compared with exercise ECG through 22 months based on one large trial of intermediate risk women (RD -9, 95% CI -14 to -4 per 100)⁸³ as well as a from a subgroup of intermediate risk patients in another trial (RD -38, 95% CI -48 to -29 per 100)⁸¹ likely indicating greater clinician confidence when stress is paired with imaging based on general understanding from accuracy studies that positive and negative predictive values are better for SPECT. In the Medicare administrative database study, both CCTA and stress echocardiography were associated with significantly higher frequency of additional noninvasive testing compared

with nuclear MPI (OR 1.52, 95% CI, 1.37 to 1.69 and 1.92, 95% CI 1.83 to 2.0, respectively) but strength of evidence is low. Studies generally did not describe posttest reclassification of risk or decisionmaking for related further testing.

Hospitalization

Cardiovascular-related hospitalizations varied somewhat across pretest risk groups across studies. There was moderate strength evidence from one large trial of low to intermediate risk ED patients that the CCTA group was significantly less likely than was the usual care group to be hospitalized or admitted for observation at the index visit (RD -26.8, 95% CI -31.9 to -21.8 per 100), but that after this visit through one month, there was no difference between (3% for CCTA vs. 2% for usual care).⁷⁷ Low strength of evidence from another large trial of intermediate risk ED patients suggested that there were fewer hospitalizations following CCTA compared with usual care at the index visit (RD -33, 95% CI -39 to -28 per 100 patients).⁷⁶ These data imply clinician confidence in the negative predictive value of the anatomic test, yet there is a predisposition of patients to return with unexplained symptoms that can be from a variety of other causes of chest pain such including vasospasm and microvascular dysfunction. By contrast, no statistical differences between CCTA and usual care were identified for acute coronary syndrome hospitalization at the index visit based on subgroups of low or high risk patients in one trial,⁷¹ but strength of evidence was low. There was moderate strength of evidence that there was no difference in cardiovascular hospitalizations between CCTA and functional testing groups in low to intermediate pretest risk ED patients within 6 months (0% in both groups) based on one trial,⁷³ and through 30 months based on one observational study⁸⁴ that compared CCTA with SPECT. Moderate strength of evidence suggested that hospitalization for cardiac causes occurred less frequently in the CCTA group compared with the exercise ECG group (RD -6.1, 95% CI -9.5 to -2.7 per 100 people) through 12 months in another trial of mixed pretest risk patients presenting to specialized chest pain clinics.⁷⁸ Two trials conducted in outpatient settings reported no differences in cardiac-related hospitalizations between groups. The strongest evidence came from the large trial comparing CCTA with functional testing, which reported no differences at a median of 25 months (RD -0.30, 95% CI -0.10 to 0.71 per 100 people)⁷²; strength of evidence was moderate. The trial of SPECT versus exercise ECG in women also found no difference between groups; strength of evidence was low.⁸³

Special Populations

With regard to evaluation of special populations, one high trial comparing CCTA with functional testing, reported that none of the prespecified subgroups modified the primary composite outcome [all-cause death, nonfatal MI, hospitalization for unstable angina, or a major procedural complication (stroke, major bleeding, anaphylaxis, renal failure requiring dialysis)], with results across subgroups consistent with those for the entire study population. Subgroups examined included age sex, race, pretest risk assessment, CAD equivalence, and pretest probability of CAD.⁷² None of the other studies identified evaluated differential effectiveness or safety. As noted above, one fair quality trial of exercise SPECT with exercise ECG in women found no differences between tests for mortality, ICA referral, revascularization, or hospitalization but did report a significantly lower use of additional noninvasive testing following SPECT.⁸³ The strength of evidence was moderate for additional testing and low for other outcomes. An additional small poor quality RCT in women compared stress echocardiography with exercise ECG reported similar frequency of a composite outcome which

included cardiac death, MI, unstable angina, or coronary angiography demonstrating 50% or more luminal narrowing (7.7% vs. 7.4%),⁸² however the strength of evidence was insufficient due to high risk of bias, lack of precision and unknown consistency. Also as noted above, a large, fair quality administrative data study in the Medicare population was identified.⁹⁶ Consistent with findings in other studies, there were no differences in adjusted effect estimates for all-cause mortality for the comparisons of nuclear MPI with stress echocardiography, exercise ECG, or CCTA. CCTA was significantly associated with increased referral for ICA and revascularization, (particularly PCI) and use of additional noninvasive testing compared with nuclear MPI; strength of evidence was low for these outcomes and comparisons.

Harms and Consequences of Testing

Harms of testing were rarely reported and details comparing harms for test were sparse with many studies stating that no harms were observed without providing further detail; 16 of the 27 comparative studies made no mention of evaluation of harms. There are no compelling safety outcomes data that can be used to recommend one approach versus another and strength of evidence was low or insufficient. No differences in major procedural complications were identified in the trial comparing CCTA with functional imaging although mild contrast reactions were significantly more common in the CCTA group than in the functional testing group (moderate strength of evidence).⁷² No differences between CCTA and usual care in bradyarrhythmia in one trial⁷⁷ or periprocedural complications in another⁷⁶ (low strength of evidence for all). A third trial reported that there was no clinical or laboratory evidence if contrast-induced nephropathy in either the CCTA or usual care group.⁷¹ One observational study reported incidental findings requiring further investigation in 7.1% of those receiving CCTA (insufficient evidence).⁸⁴ Evidence from observational studies regarding test related harms and impact of incidental findings following CCTA was insufficient to draw conclusions.

A important patient safety concern is exposure to low to moderate levels of ionizing radiation related to noninvasive testing that add to cumulative lifetime radiation exposure. To the extent that noninvasive tests for CAD reduce the need for conventional angiography, cumulative exposure might be reduced. To the extent that they result in the need for additional testing, it may be increased. The true attributable risk from radiation-based diagnostic tests cannot be determined. Some experts consider the potential for harm from radiation exposure (either deterministic or stochastic) to be clinically significant particularly given that patients may be likely to have additional tests using radiation over many years. Estimates of radiation exposure from included studies are provided in Appendix G (Table G4) and the introduction provides contextual information on radiation exposure ranges for testing. Radiation exposure from included studies for initial testing strategies ranged from 3.8 to 17 mSv for CCTA and 10.5 to 38 for SPECT. One study reported a mean of 4.0 mSv for positron emission tomography (PET)⁸⁹ and another study⁷⁶ reported a mean of 4.7 mSv for usual care. Consideration of cumulative radiation exposure related to downstream testing and intervention is important when discussing the benefits and consequences of the different noninvasive tests and their contribution to lifetime radiation exposure. Higher mean cumulative radiation accounting for additional testing was seen in single trials following CCTA compared with usual care (14.3 ± 10.9 vs. 5.3 ± 9.6 mSv)⁷⁶ and functional testing (12.0 ± 8.5 vs. 10.1 ± 9.0 mSv)⁷². One study reported higher cumulative exposure for following CCTA versus SPECT in patients referred for ICA (medians, interquartile ranges, 15.2 mSv, 12.7 to 17.1 vs. 10.8 mSv, 10.2 to 11.7).⁹⁸ By contrast, another trial reported lower cumulative exposure for additional testing following CCTA versus SPECT (medians,

interquartile ranges 7.3 mSv, 5.1 to 13.7 vs. 13.3 mSv, 13.1 to 38.0).⁸⁰ One observational study of CCTA and exercise ECG reported higher exposure for index and downstream testing for CCTA for those who tested negative as well as those who tested positive or whose tests were inconclusive, however among those who tested positive who had revascularization, mean cumulative exposure was slightly higher in the ECG group (28 vs. 32 mSv).⁹⁴ Consideration of patient preferences with regard to the impact of radiation exposure should be part of shared decision making around noninvasive testing.

Findings in Relationship to What is Already Known

Few prior reviews have evaluated the impact of noninvasive testing on clinical and management outcomes. Systematic reviews and studies on noninvasive testing for coronary artery disease identified from our search focused on traditional measures of test performance (e.g., sensitivity, specificity) compared with ICA. They generally did not directly compare the effectiveness and safety of different modalities with regard to impact on clinical outcomes specifically in the population of interest in this report. Consistent with this review, prior systematic reviews^{119, 120} have reported few or no comparative studies evaluating the impact of noninvasive tests on clinical outcomes, decisionmaking, or use of additional testing and note that harms are rarely reported; relevant studies from these reports were included in this systematic review. The recent Agency for Healthcare Research and Quality (AHRQ) report on noninvasive testing in women reported that there was insufficient evidence from three studies that treatment decisionmaking and clinical outcomes were impacted by noninvasive testing.¹²¹ Consistent with our report, there were no differences in clinical events or hospitalization in studies comparing noninvasive tests. They also concluded that studies were underpowered to detect clinical outcomes.

Applicability

There are a number of factors that impact the applicability of this report's findings.

Patients

Eight of the 13 trials identified were in patients presenting to the ED with CAD symptoms, however the largest trial was in an outpatient setting. Patients presenting to the ED represent a broad spectrum of pretest risk probabilities including those at low or intermediate risk as well as those at high risk for CAD. The severity, newness and duration of symptoms may differ from those seen in outpatient settings, who generally present with more mild to moderate symptoms. Definitions of pretest risk varied across included studies and some did not report or stratify by pretest risk, making it difficult to fully evaluate results based on pretest risk across settings. It is likely that the patients enrolled in the included studies are representative of those in the broad range of clinical practice.

Interventions and Comparators

The evidence may be skewed toward newer testing modalities and studies of established tests may not reflect current technology and diagnostic performance. CCTA was the most common noninvasive test assessed, accounting for 48% of included studies. This may be because CCTA is a newer modality and thus is compared with established tests, such as stress echocardiography and

myocardial perfusion imaging. Few studies comparing different types of functional testing, particularly between established functional tests such as stress echocardiography, exercise ECG and nuclear stress testing were identified. A recent systematic review suggests that over the past two decades, substantial decline was seen in investigations related to echocardiography and nuclear cardiology compared with marked increase in cardiac CT imaging studies.¹²² Input from clinical team members and the Technical Expert Panel (TEP) suggests that there is substantial variation in clinical practice with regard to which test may be ordered as an initial test based on patient presentation, testing availability and clinical perspective. Thus, it is not clear to what extent CCTA may or may not be the initial noninvasive test for first-line evaluation of symptomatic patients without known CAD after a resting ECG and therefore impact the applicability of this report. None of the included studies included a no testing arm. To the extent that clinical decision making is done based on clinical evaluation and judgment without testing findings in this report may be less applicable to settings where testing is not routinely done.

Outcomes

Findings related to rare outcomes of death, MI or hospitalization may not be fully applicable to broader clinical populations in part due to small study sizes and inability to fully characterize such outcomes, particularly over the longer term. Moreover, the impact of a negative test or the treatment downstream from a positive test may extend beyond traditional major adverse coronary events to quality of life, reduction in symptoms, and level of activity. These outcomes have not been examined in the majority of included studies. The majority of trials reported outcome at the time of an index ED visit. The clinical management objectives in an ED setting are somewhat different than in an outpatient setting.

Settings

Most RCTs were conducted in the ED to help determine immediate disposition for discharge or additional evaluation and/or hospitalization. The initial goal is to make a diagnosis for the cause of chest pain in order to inform appropriate treatment and next steps at the index visit; thus, MI reported at the index visit may reflect a test's ability to make the diagnosis for immediate decisionmaking but does not reflect the tests' ability to impact future clinical outcomes. Testing is only able to affect events after the index visit and long term follow up from ED studies was limited. Thus the applicability of findings from ED studies to general outpatient settings over the long term is likely limited.

Implications for Clinical and Policy Decisionmaking

The 2012 American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) guideline states that diagnostic testing is most valuable when the pretest probability of ischemic heart diseases is intermediate (10% to 90%) and provides a range of options for which test may be used in a given scenario however the effectiveness of different modalities with regard to impact on clinical outcomes are not compared.⁸ Currently, a variety of tests as the initial (and additional) diagnostic tests for patients at intermediate pretest risk of CAD are employed and there is uncertainty regarding which tests, if any, may be most suitable and beneficial in patients who present with symptoms suggestive of CAD but have no prior history of it. Although several ACCF/AHA Appropriate Use Criteria (AUC) are available, including the 2013 multi-modality imaging AUC,¹²³ they do not explicitly compare multiple NIT modalities

nor do they make specific recommendations for timing/sequencing of tests or for repeat testing based on pretest risk group.

Low to moderate strength of evidence from eight trials suggests there is no clear difference in MI or all-cause mortality between different testing strategies across settings and pretest risk grouping which included those at intermediate risk; possible contributors to this finding, including lack of power to detect a difference, were previously described. Information from two studies that provided data on low and high pretest risk (without ACS) groups do not provide insight into best testing strategies in those groups and the strength of evidence was insufficient for the few outcomes reported and no conclusion can be drawn. Across studies that enrolled intermediate-risk group, no clear benefits of one testing strategy versus another were seen and no clear picture of harms for various tests was available from included studies. One apparent trend uncovered by the review is that tests that evaluate coronary anatomy such as CT result in a greater likelihood of referral for ICA and subsequent intervention than functional tests; however, the strength of evidence varied from high to low depending on the comparator and the impact on clinical outcomes is not known as most studies do not present data on treatments administered to individual study participants. Thus, it is not clear if the increased referrals were helpful or not with regard to influencing clinical outcomes. Only two studies provided limited information on the overall impact of testing and resulting treatment strategies on patient symptoms and quality of life. No studies that compared testing to an arm that received no testing were identified, so the impact of any of the noninvasive testing pathways over clinical evaluation is not known.

As defined in the ACCF/AHA guidelines, the intermediate pretest group is broad and heterogeneous (10% to 90%) and in the absence of information on posttest risk, the value of the various tests for influencing important management decisions at each end of the spectrum is not clear. Various ACCF appropriate use criteria^{20, 124-126} and guidelines provide do provide general recommendations for testing and treatment. For example, a 25 year-old woman who is a current smoker with atypical chest pain would have a low pretest risk. Her pretest probability of obstructive coronary artery disease is low. Performance of an imaging cardiac stress test would be considered inappropriate or rarely appropriate¹²⁴; an exercise ECG test could be performed, but would be graded a IIb recommendation.²⁰ If this were a 45 year-old woman with history of smoking she would be intermediate risk for obstructive coronary artery disease and it would be appropriate for her physician to order a stress echocardiogram¹²⁴ or similar test.

In general, next steps following a positive result from an initial noninvasive test is in part based on the posttest annual predicted rate of cardiac mortality as described in the 2012 ACCF/AHA guideline: low risk (<1% per year), intermediate risk (1% to 3% per year), or high risk for cardiac mortality (>3% per year).⁸ Clinical presentation and test results are both considered in this determination. A positive test can trigger treatment with guideline directed medical care, or if high risk, can precipitate a coronary angiogram and consideration for revascularization. In general, people who would be categorized as being at low risk (test result is negative) or intermediate risk and who do not exhibit characteristics of acute coronary syndrome medical management may be appropriate. In most instances, patients in these categories can be managed without invasive assessment. In the case of the 45 year old woman above, based on a normal exercise echocardiogram then she is reclassified as low risk and predicted to have an annual event rate of cardiac death or nonfatal myocardial infarction of less than 1 percent.¹²⁶ Treatment of high blood pressure and smoking cessation would be appropriate; but further diagnostic evaluation would not be warranted unless there was a change in clinical status. If this patient had an abnormal stress test which was intermediate risk medical therapy for CAD in

addition to comorbidities would be appropriate; proceeding to angiogram would be at the discretion of the physician¹²⁵ through a shared decision making process. In patients who are considered to be at high risk based on noninvasive testing and presentation, invasive coronary angiography for further risk stratification and assessment of appropriateness for revascularization may be the next logical steps. In general, indications for revascularization are based on the clinical presentation (acute coronary syndrome or stable angina), the severity of the angina (based on Canadian Cardiovascular Society Classification), the extent of ischemia on noninvasive testing, and the presence or absence of other prognostic factors including congestive heart failure, depressed left ventricular function, and diabetes, the extent of medical therapy, and the extent of anatomic disease.^{127, 128} However, it is considered appropriate for a symptomatic patient with a high pretest probability of obstructive coronary artery disease to undergo stress imaging for diagnostic or prognostic reasons.¹²⁴ In either case appropriate medical therapy for comorbidities and suspected coronary artery disease with anti-anginal agents in addition to aspirin and statin therapy would be prescribed.

From the included studies, however, it is not clear how posttest risk was assessed, if these or other pathways were followed after the initial test, which test may lead to the most appropriate treatment give the posttest risk or whether the treatments impacted outcomes. While the various ACCF/AHA guidelines an appropriate use criteria provide a range of options for which test may be used in a given scenario and treatment initiated, the effectiveness of different testing modalities leading to appropriate treatment are not compared with regard to impact on clinical outcomes.

In the absence of high-strength evidence regarding testing options, including the possibility of not testing, decisions must necessarily be made on the basis of other factors related to the initial test and beyond. The ability of a test to accurately diagnose treatable CAD is important; so too are the costs and consequences beyond the initial test such as followup of false negative results (e.g., tests with high false positive rates in a low pretest risk population) and the costs and consequences of missing significant disease (e.g., dismissal of patients with CAD needing treatment from the ED). The costs and consequences depend to some extent on the role a test plays in the diagnostic work up pathway as well as the availability and convenience of a test. Consequences of testing that need to be considered include those related to patient anxiety and patient quality of life and those related to radiation exposure of the index test as well as potential downstream exposure from additional testing resulting from the initial test and future testing and/or treatment. Consideration of patient preferences, based on their understanding the range of consequences of initial and downstream testing, is an important part of shared decisionmaking for initiating noninvasive testing.

Limitations of the Systematic Review Process

This review has some potential limitations. In keeping with the intent of key questions, stratifying by pretest risk may have resulted in fewer studies to pool and leaving single studies for most comparisons. This, combined with substantial heterogeneity in how pretest risk was defined, the time frames over which outcomes were evaluated and clinical heterogeneity between tests evaluated, there were too few studies for head to head meta-analysis for most outcomes and network meta-analysis was not feasible. Variable reporting on patient symptoms and characteristics related to CAD risk precluded application of a standardized method for calculating or assigning pretest risk across studies. In light of this, test comparisons were evaluated according to pretest risk as specified by authors to discern patterns within and across

pretest risk levels and setting to qualitatively synthesize outcomes where pooling wasn't possible. This resulted in limited ability to truly examine the evidence by pretest risk. Inclusion was restricted to studies published in English; however, this is not likely to have impacted the evidence base as few non-English language studies of potential were seen in the searches. Formal, statistical assessment of reporting and publication bias was not possible, however we did consult published study protocols, solicited and evaluated Scientific Information Packets (SIPs) and searched ClinicalTrials.gov to investigate the possibility of such bias. Given the paucity of RCTs, comparative observational studies were included and despite a focus on outcomes where authors controlled for confounding, there is a possibility that residual confounding influenced reported results, lowering confidence in effect estimates. Comparative studies included may not adequately capture harms safety issues in the population of interest. The focused criteria on inclusion of studies comparing established first-line test (beyond a resting ECG) narrowed the review scope substantially, but was felt to provide a clearer approach to addressing the areas of uncertainty described in the introduction. It is possible that older, historical studies outside of our population of interest provide more detailed information about the safety of various tests, particularly more established tests. There were too few studies of any given comparison to meaningfully evaluate publication bias. Where available, protocols of trials were reviewed to consider the extent to which outcomes were reported selectively and information from Scientific Information Packets requested from stakeholders was evaluated; while overt publication bias was not detected, there is always the possibility it may be present. This review provides a snapshot of currently available evidence on the questions posed. Included studies may not reflect technological advances that have been made in the various testing modalities.

Limitations of the Evidence Base

Important limitations of the evidence base include the paucity of studies that compared the impact of different noninvasive tests on hard clinical outcomes such as mortality and myocardial infarction; few RCTs were available, in particular for comparisons of established functional tests in the population of interest. No trials that included a no testing arm were identified. Methods for assessing pretest risk, defining cardiovascular outcomes, and defining usual care were poorly reported and not standardized. The variable methods for determination and classification of pretest risk across studies and inability to implement a standardized method for assessing pretest risk across studies precluded detailed evaluation of testing strategies by pretest risk level to determine the comparative values of tests for a given pretest risk. The intermediate risk range is broad (10% to 90%). Studies did not provide information on the impact of test results on posttest risk stratification or clinical decision making for treatment or further testing precluding evaluation of the impact of testing in this group. Some studies reported composite cardiovascular outcomes, which can be misleading depending on the effects on the individual components.¹²⁹ Studies did not evaluate aspects of unnecessary testing. Reporting of harms was suboptimal; 16 of the 27 comparative studies made no mention of evaluation of harms and another three merely stated that there were no adverse events and with the exception of one study, authors reported few details about harms. As mentioned previously, study sample sizes and short-term followup may preclude evaluation of rare events. Studies did not describe the impact of testing on treatment choices. Few studies on PET, CACS and establish tests such as stress echocardiography were identified.

Research Gaps and Recommendations

The gaps in the available evidence are many and include:

- Lack of studies that compare testing and resultant treatment strategies to clinical evaluation (and resulting treatment strategies) without testing. This is particularly important in those at very low or low pretest probability.
- Lack of a standardized approach to determining and reporting pretest risk across studies; variable definitions of pretest risk precluded ability to effectively stratify by pretest risk.
- The large range of pretest likelihoods across studies precluded detailed evaluation of the impact of testing on clinical decision making or outcomes for those that are at the lower end of the range and those at the higher end. Future research should use risk models that further refine the range of pretest probability for those at intermediate risk (e.g., The Duke Clinical Score) to delineate the impact of testing on clinical decision making at the lower and higher ends of the range. Tools that refine the range may also be clinically useful.
- There is insufficient information from included studies on the comparative impact of tests on posttest risk stratification.
- There is limited high-quality comparative evidence linking established tests with clinical outcomes and decisionmaking in the population of interest by pretest risk, particularly in nonemergent settings and over the longer term. Studies describing outcomes at the index ED visit do not allow conclusions regarding the impact of testing on clinical outcomes.
- No studies evaluated issues of unnecessary testing or treatment.
- There is limited information on the impact of testing on treatment decisions, including those related to use of medical therapy, and downstream testing including followup of false negative tests and impact of missed disease. It is not clear whether the individuals that would most benefit from a given treatment strategy were referred to those strategies and whether the strategies were effective.
- There is limited evidence on the best testing strategy for posttest risk stratification for discerning which patients may be at highest risk and may benefit most from various treatment strategies.
- There is limited evidence on the impact of testing strategies (including consequences of downstream testing and treatment) on patient related outcomes such as quality of life and symptom status.

There is a need to enhance the evidence linking testing strategies and clinical pathways to clinical outcomes. Few trials listed on ClinicalTrials.gov appear to be active or pertain to symptomatic patients without known CAD (Appendix K). To determine optimal testing strategies and roles of tests in different pretest risk groups, several issues should be addressed in future research. First, use of standardized risk models that refine and narrow the currently broad “intermediate” risk group are needed. For example, because healthcare trends to streamline and reduce the cost of care, newer risk models such as the Duke Clinical Score have narrowed the intermediate range and tend to reclassify many of those classified as “intermediate risk” in the Diamond-Forrester model to “low risk”.¹³⁰ Documentation of posttest risk stratification and its impact on clinical management (treatment and referral for additional testing) needed to determine optimal testing strategies and roles of tests in different pretest risk groups. This may facilitate comparison of tests to effectively parse out patients at the highest risk end and those at

the lower risk end and evaluation of the impact of management decisions in these groups as they likely will differ. Documentation of management of those who test positive compared to those who test negative and followup of these groups for sufficient time to evaluate clinical outcomes is needed. These factors should be considered for all future comparative studies. RCTs, including pragmatic trials which attend to these issues and have sufficient power to detect differences in clinical outcomes are desirable. Prospective cohort studies that address selection bias and confounding by indication in addition to those related to the issues above have the potential to enhance the evidence base and may be more feasible for some settings. Studies comparing testing to clinical evaluation without testing are would provide valuable information on the impact of testing in general and are much needed to help assess the need for testing and possible overuse of testing. Comparative studies (RCTs or prospective cohorts) of functional tests that reflect technological advances as applied to symptomatic patients without known CAD would update the evidence base. Meta-analysis of patient-level data from existing trials may allow for more specific stratification by pretest probability or specific risk factors. Studies documenting how specifically test results influence decisionmaking regarding further testing and treatment strategies and follow-patients to evaluate the impact of the testing pathway would provide important insights into the overall impact of testing on long term outcomes. Future research also needs to incorporate evaluation of patient-centered outcomes.

Conclusions

There were no clear differences between testing strategies across settings with regard to clinical or management outcomes to recommend one strategy over another for any given pretest risk group that included intermediate pretest risk patients. No conclusions regarding low-risk patients or those without acute coronary syndrome at high risk are possible. Limited evidence from randomized controlled trials found no clear differences between coronary computed tomography angiography versus other strategies in clinical outcomes across risk groups, though anatomic testing may result in a higher frequency of referral for invasive coronary angiography and revascularization. The absence of information on posttest risk stratification and subsequent decision making precluded evaluation of the impact of testing on patient management or outcomes of management. Testing strategies vary in radiation exposure; there is inadequate comparative evidence to make judgments regarding exposure for initial test or downstream testing. Assessment of harms was limited. Future research using more refined, evidence-based definitions of pretest risk coupled with information on posttest risk stratification, its impact on clinical management (treatment and referral for additional testing) and longer term follow up to assess clinical outcomes are needed to determine optimal testing strategies and roles of tests in different pretest risk groups.

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Abbreviations and Acronyms

ACCF	American College of Cardiology Foundation
ACS	Acute coronary syndrome
AHA	American Heart Association
AHRQ	Agency for Healthcare Research and Quality
BMIPP	Beta-methyl iodophenyl pentadecanoic acid
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CCTA	Coronary computed tomography angiography
CER	Comparative Effectiveness Review
CMR	Cardiac magnetic resonance
CT	Computed tomography
EBCT	Electron beam computed tomography
ECG	Electrocardiography
FDG-PET	Fludeoxyglucose (18F) positron emission tomography
FDA	Food and Drug Administration
FFR	Fractional flow reserve
F/U	Followup
HIV	Human immunodeficiency virus
ICA	Invasive coronary angiography
IQR	Interquartile range
KQ	Key Question
LBBB	Left Bundle Brach Block
LVEF	Left ventricular ejection fraction
MDCT	Multidetector computed tomography
MI	Myocardial infarction
MPI	Myocardial perfusion imaging
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
MUGA	Multigated acquisition scan
NA	Not applicable
NR	Not reported
NS	Not statistically significant
NSTE-ACS	Non-ST elevation acute coronary syndromes
NSTEMI	Non-ST-segment elevation myocardial infarction
PCI	Percutaneous coronary intervention
PET	Positron emission tomography
PTCA	Percutaneous transluminal coronary angioplasty
RCT	Randomized controlled trial
RD	Risk difference
RR	Relative risk
SD	Standard deviation
SPECT	Single photon emission computed tomography
STEMI	ST-segment elevation myocardial infarction
TEE	Transesophageal echocardiography
TEP	Technical Expert Panel

